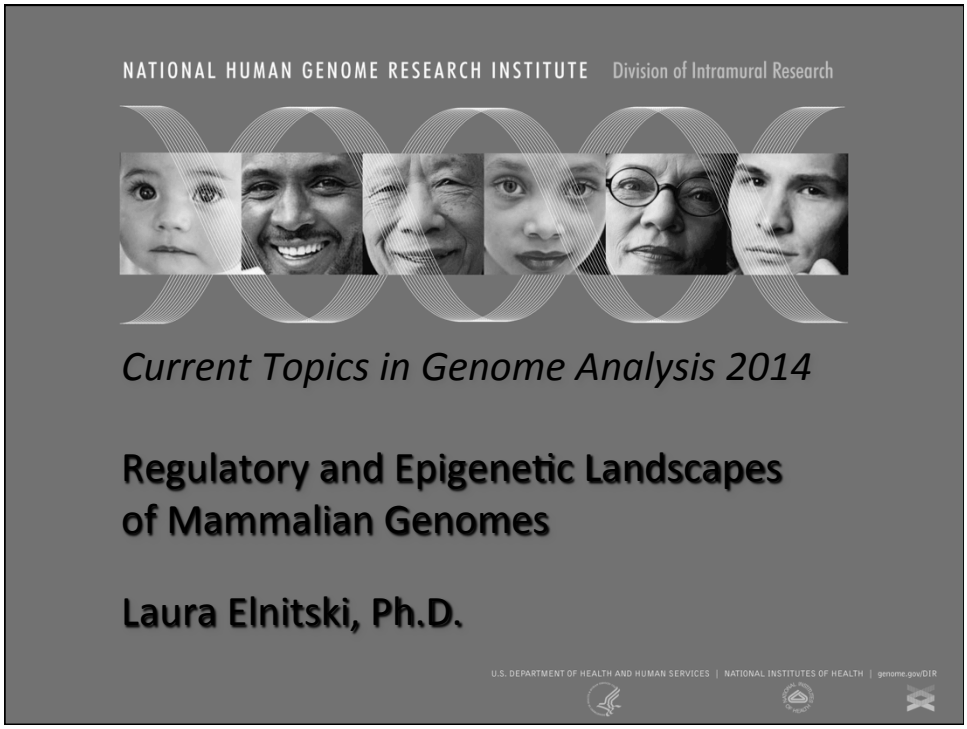


JOHNS HOPKINS
MEDICINE
CONTINUING MEDICAL EDUCATION

Current Topics in Genome Analysis 2014

Laura Elnitski, Ph.D.

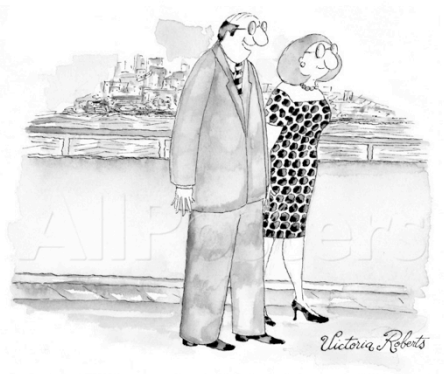
No Relevant Financial Relationships with Commercial Interests

From blueprint to implementation

I. Genome composition

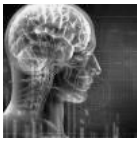
II. Enhancer studies

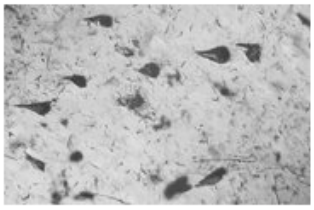
III. Epigenetics



"What ever will we think about now that the genome project is almost complete?"

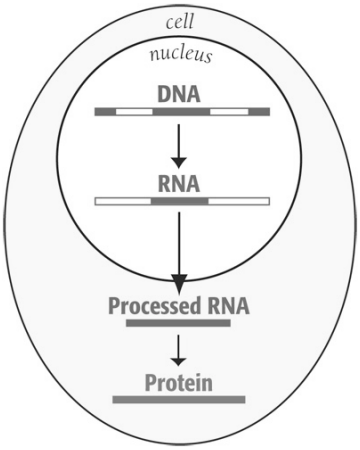
Genomics spurs rapid advancement





An image of tau tangles in the brain, often a hallmark of Alzheimer's disease. A group of researchers has found that a protein, normally active in fetuses, may also protect the neurons in older people.
Yankner laboratory

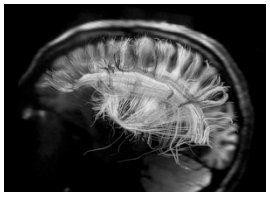
Central dogma - 1958



Mutations identify Mendelian diseases

Gateway to personalized medicine

June 26, 2000



Brain Mapping Project

Baby Genome

TCGA

Disease risk associations

Personalized medicine

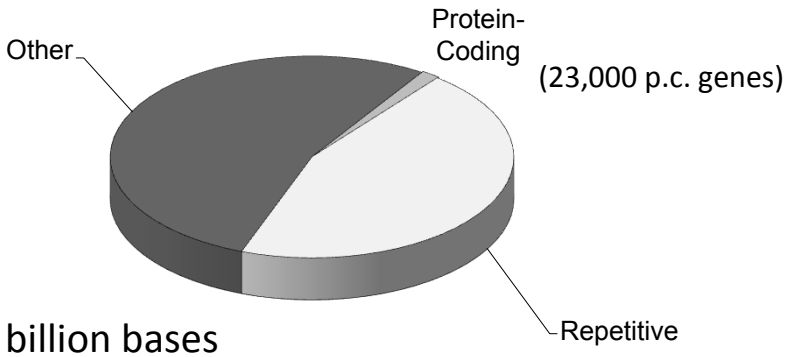
$1000 genome

I. Genome composition

From blueprint to implementation

"the genome comes alive in 3D"

Characterizing the Human Genome



~ 3.3 billion bases

DEBATES

HOW MUCH OF THE GENOME IS FUNCTIONAL?

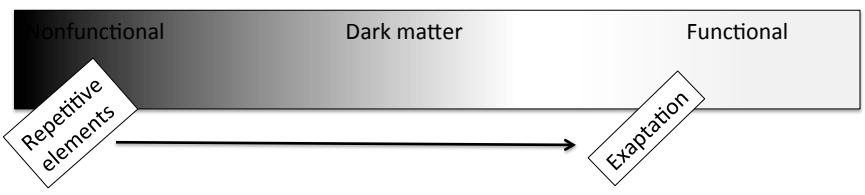
HOW MUCH OF THE GENOME IS SUPERFLUOUS?

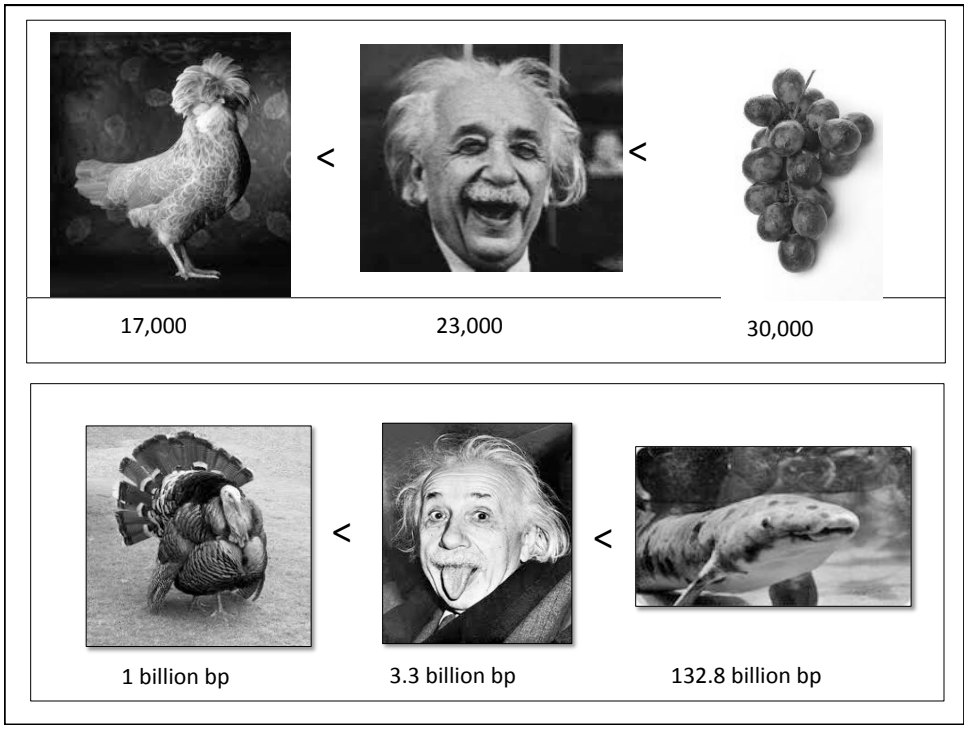
how to be sure?

HOW WELL CAN WE DISTINGUISH THE TWO?

biochemical signals, conservation, genetic evidence

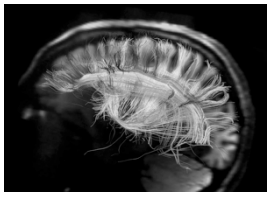
The 98%

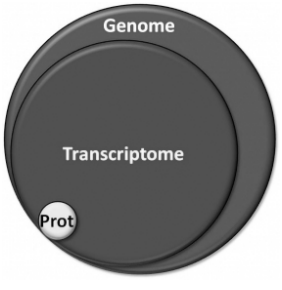




Complexity

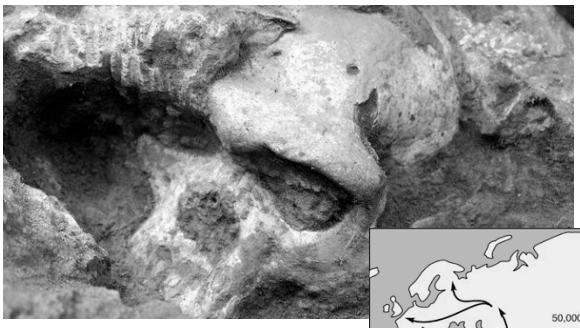
- Cell-type diversity
- Coding genome
  - Alleles
  - Splicing isoforms
  - Regulated translation
  - Posttranslational modifications
- Noncoding RNA
- Noncoding genome
  - Alternative promoters
  - Alternative 3' UTRs
  - Myriad enhancers
  - Intronic regulatory elements
  - Replication origins
- Epigenetic modifications



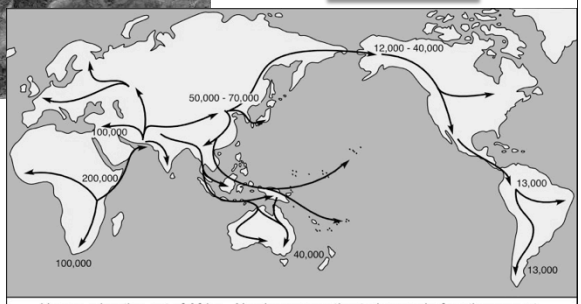


www.dkfz.de

Hominid History



Georgian National Museum



Human migration out of Africa. Numbers are estimated years before the present.

bonner@indiana.edu

FUN USES OF THE GENOME

Genome challenges

Thea Norman (Official Rep) 4 months ago

Welcome to the ICGC-TCGA-DREAM Somatic Mutation Calling Challenge

The Undiagnosed Diseases Program

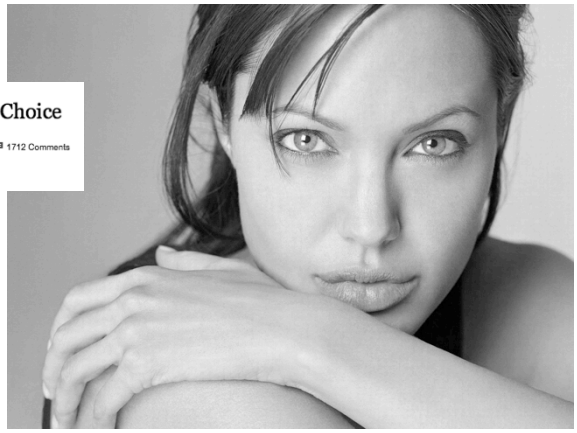
- Overview
- Program Background
- Program News
- Program Contact

OP-ED CONTRIBUTOR

My Medical Choice

By ANGELINA JOLIE
Published: May 14, 2013 | 1712 Comments

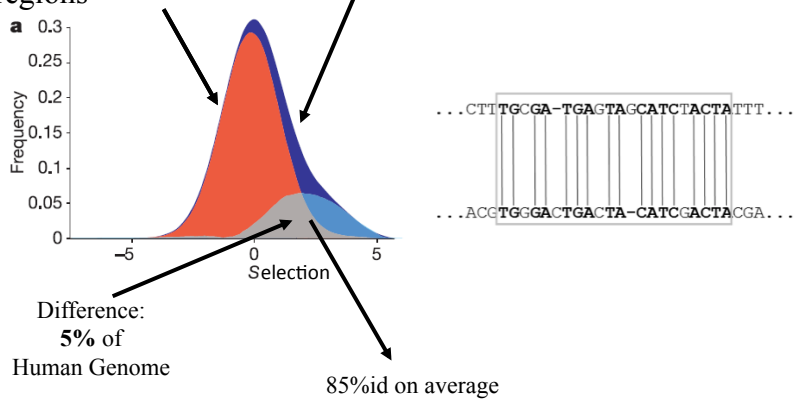
LOS ANGELES



Conserved elements in the human genome

alignments in neutral regions

all human-mouse alignments

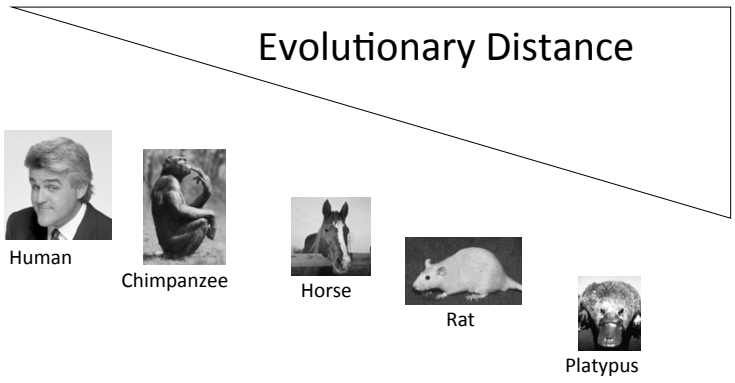


Difference: **5%** of Human Genome

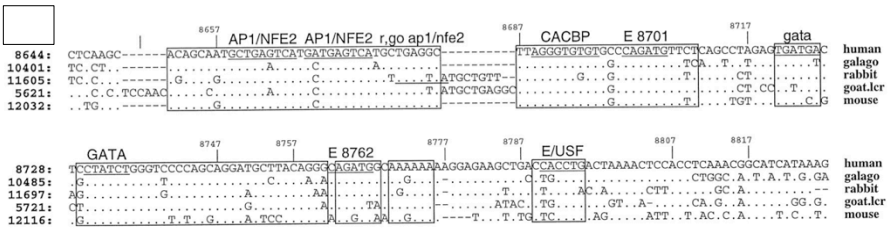
85%id on average

[Mouse consortium, 2002]

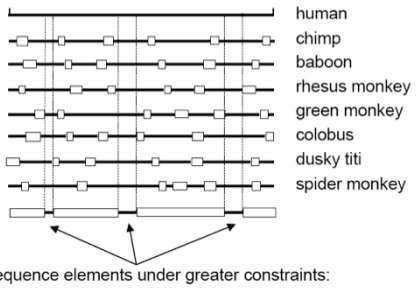
EVOLUTIONARY CLUES



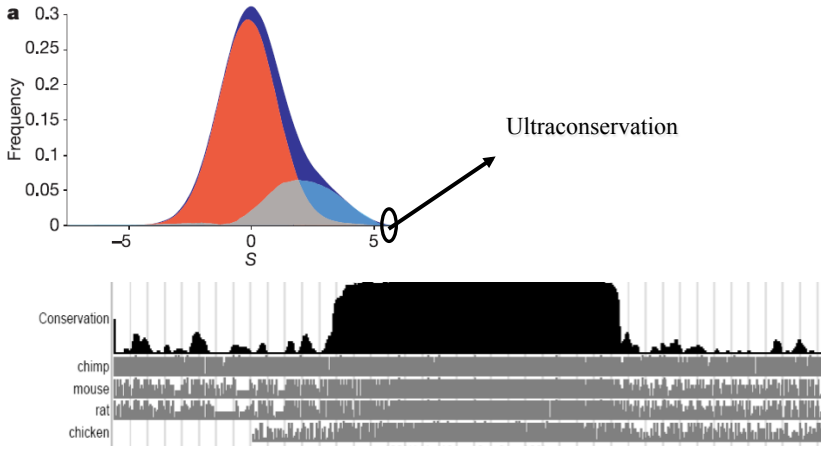
Phylogenetic footprints



Phylogenetic shadowing

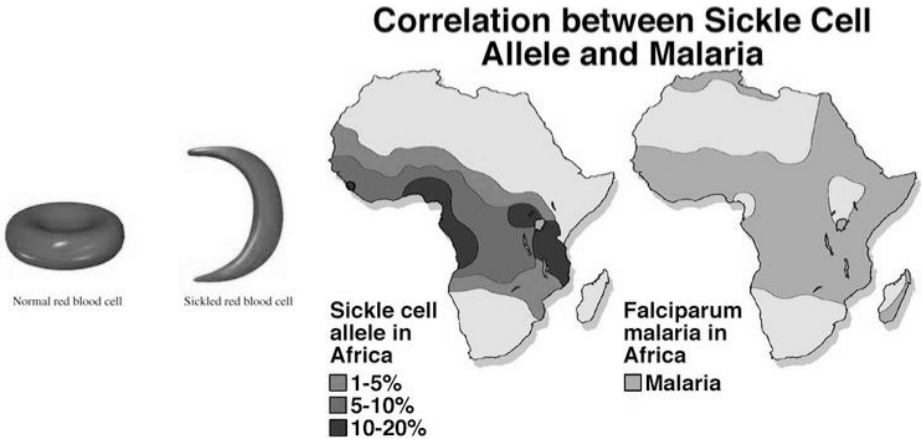


Ultraconserved elements in the human genome



UCSC browser conservation track

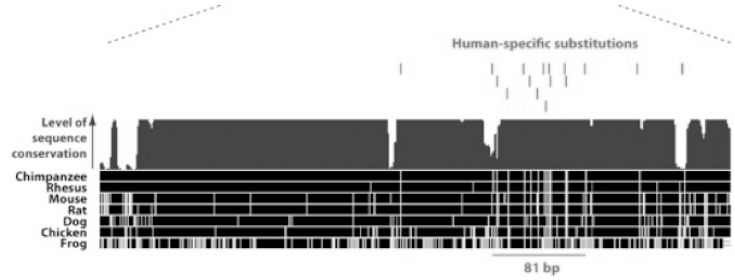
Function through variation

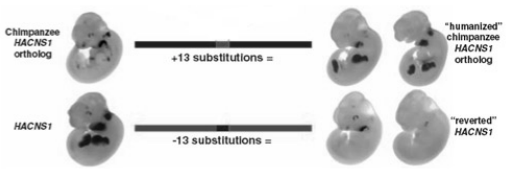


The McGraw-Hill Companies

Lactose intolerance

Human accelerated regions

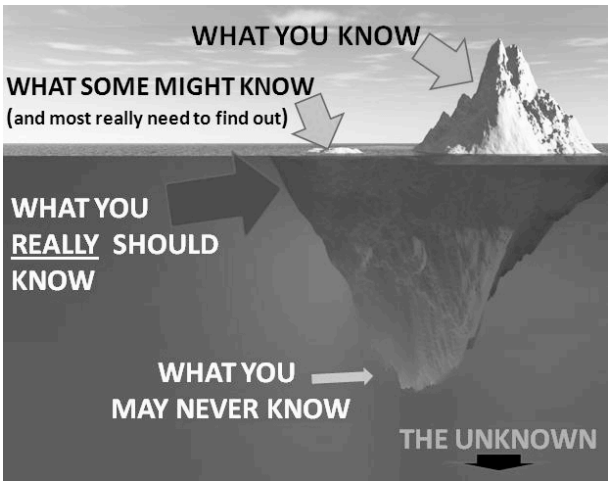




Processes in accelerated change

-
-
-

ELUSIVE GOALS



Genome sequence

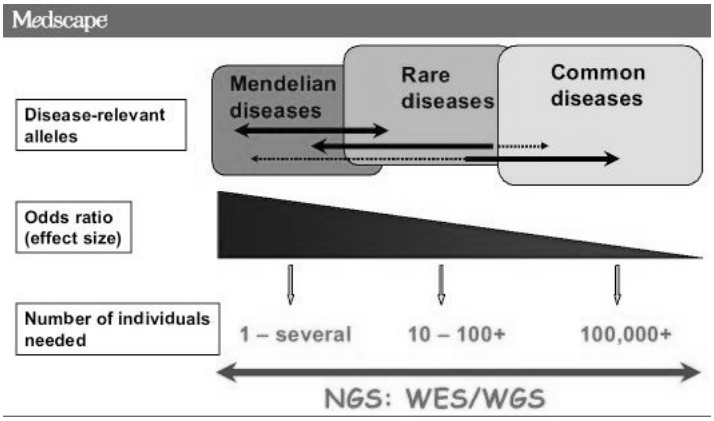
Functional sites

Noncoding RNAs

Role of DARK MATTER

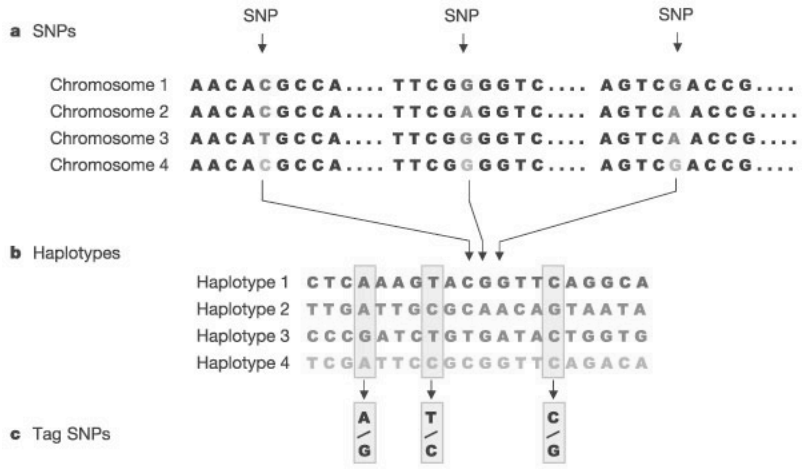
We don't know how much we don't know

Understanding disease mechanisms



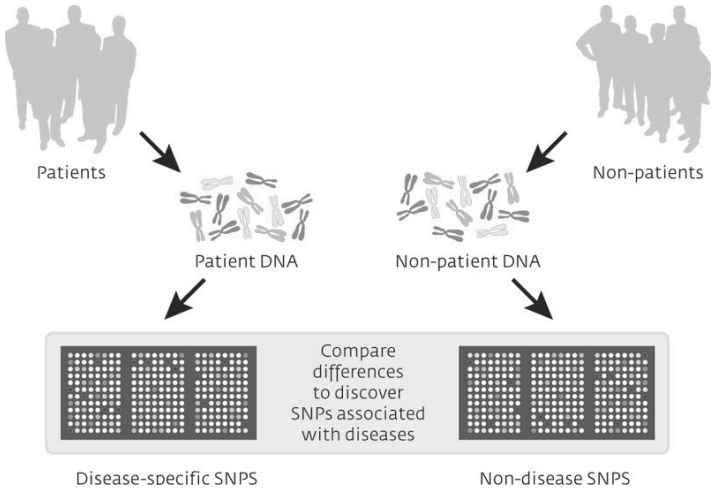
J Med Genet. 2011;48:580-589.

Genotyping for common variants



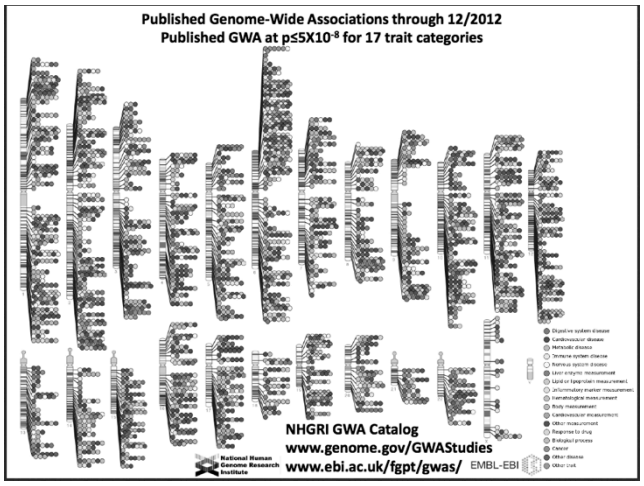
http://hapmap.ncbi.nlm.nih.gov/whatishapmap.html

Genome wide association studies

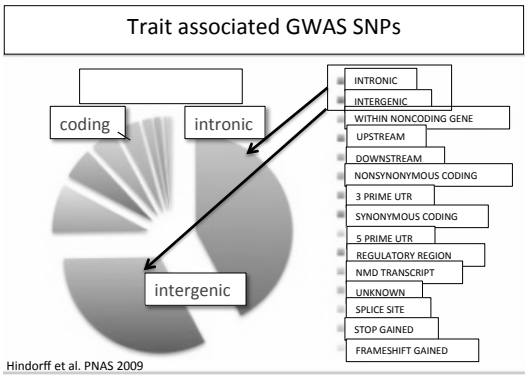


http://www.mpg.de/10680/Modern_psychiatry

GWAS loci



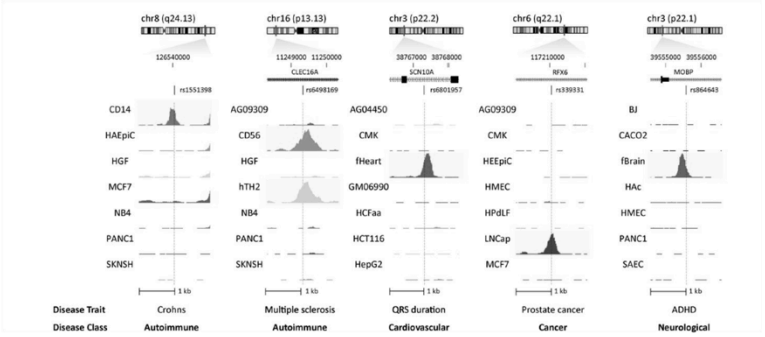
GWAS findings in noncoding regions



Hindorff et al. PNAS 2009

II. Enhancer studies

Disease-associated variation clusters in pathogenic or target cell types

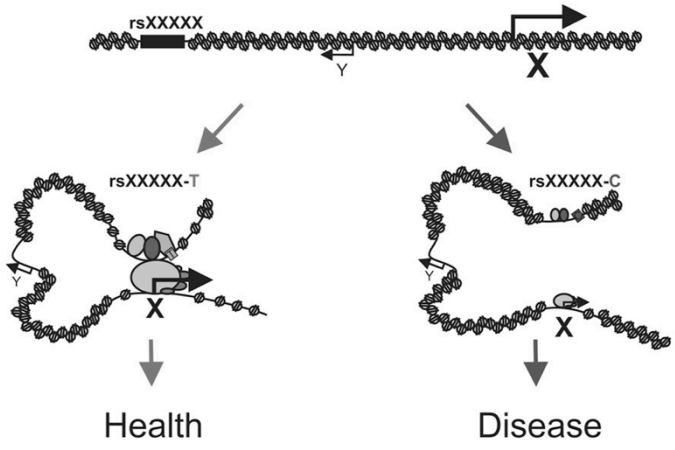


A significant fraction of GWAS variants falling in regulatory DNA directly affect TF occupancy

Maurano et al., Science 2012

Putative effect of variants in enhancers

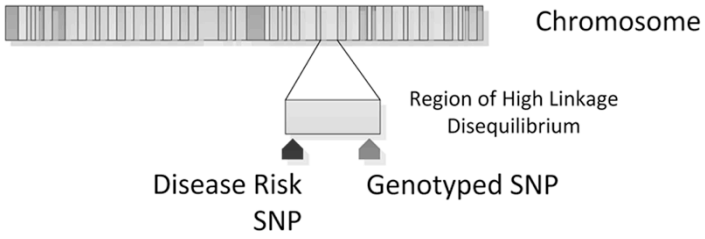
Allele Specific activity



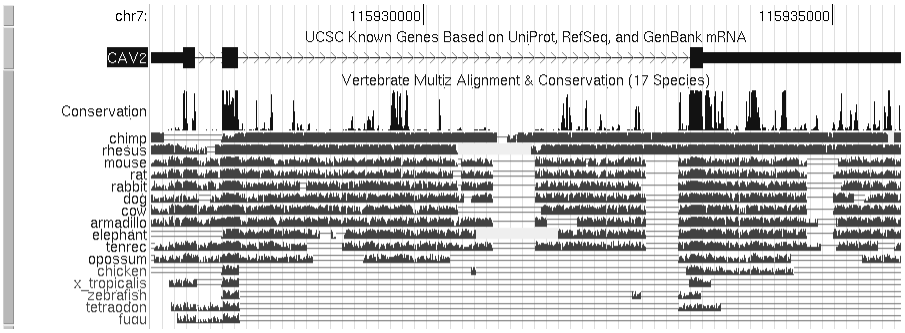
Front. Genet., 28 September 2012

GWAS caveats

Indirect Association



Predicting function in the genome

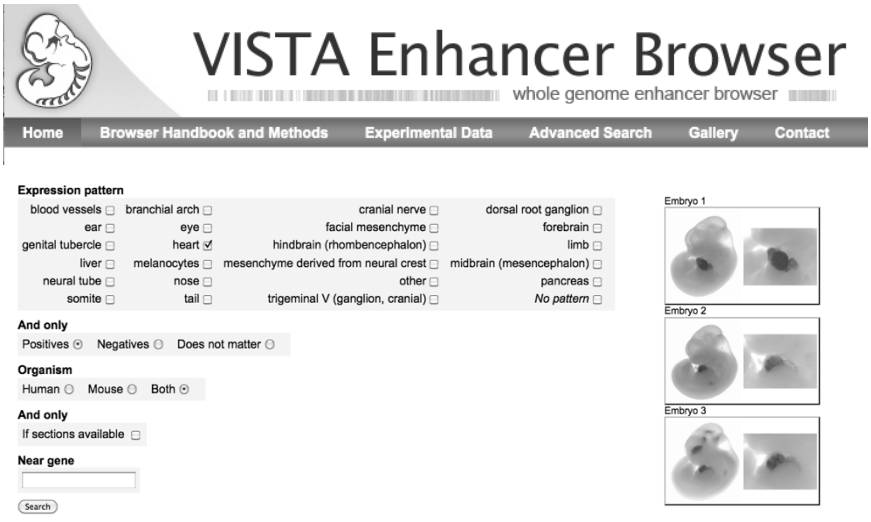


Mutations in functional DNA are less likely to be tolerated

Determining biochemically active regions

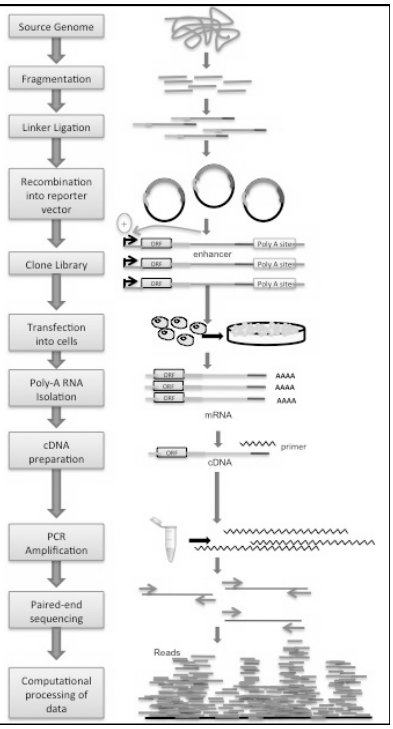
- Transcription factor occupancy
- DNase Hypersensitivity
- FAIRE data
- Chromatin modifications

Validation using transgenic mice

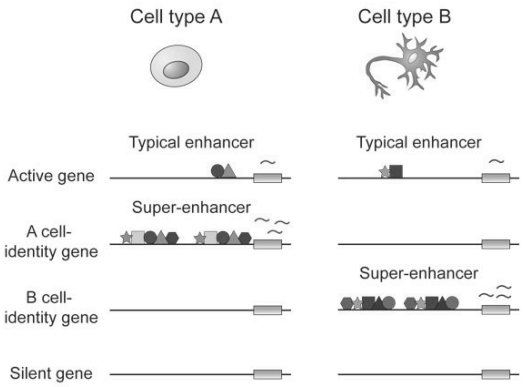


STARR-Seq

- High throughput enhancer assay

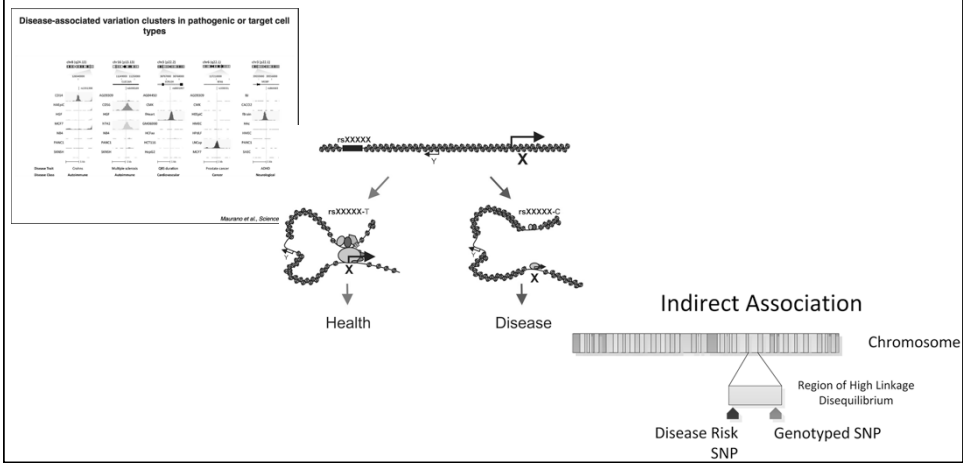


Super & Stretch Enhancers

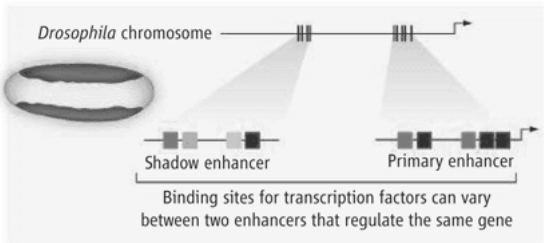


ENCODE catalogs

~ 50% of predicted functional elements don't test positive in an enhancer assay



Shadow enhancers (redundancy/resilience?)



Science 5 September 2008:
vol. 321 no. 5894 1300-130

Deletion of candidate elements

Deletion of Ultraconserved Elements Yields Viable Mice

Nadav Ahituv[1,2¤], Yiwen Zhu[1], Axel Visel[1], Amy Holt[1], Veena Afzal[1], 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 … in vivo, we removed four noncoding ultraconserved elements (ranging in length fr… he mouse genome. To maximize the likelihood of observing a phenotype, we chose … as enhancers in a mouse transgenic assay and that are near genes that exhibit marke… ely inactivated in the mouse and when their expression is altered due to other genomi… ur resulting lines of mice lacking these ultraconserved elements were viable and fe… cal abnormalities when assayed for a variety of phenotypes including growth, longe… In addition, more targeted screens, informed by the abnormalities observed in mic… he investigated elements had been altered, also failed to reveal notable abnormaliti… ve of all the possible phenotypic impact of the deleted sequences, indicate that ex… ot necessarily reflect crucial functions required for viability.

GWAS summary

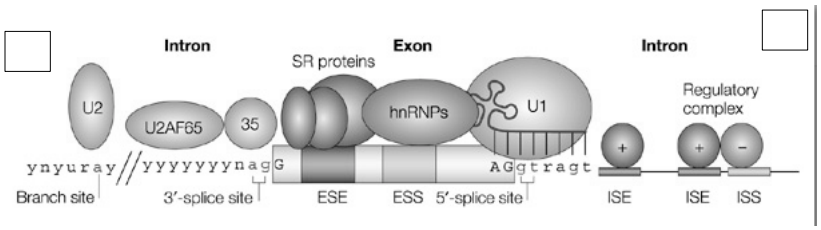
- Resounding success
- Modest effects (OR < 2)
- Substantial heritability remains to be explained

Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease

Manuel A Rivas[1–3], Mélissa Beaudoin[4,23], Agnes Gardet[5,23], Christine Stevens[2,23], Yashoda Sharma[6], Clarence K Zhang[6], Gabrielle Boucher[4], Stephan Ripke[1,2], David Ellinghaus[7], Noel Burtt[2], Tim Fennell[2], Andrew Kirby[1,2], Anna Latiano[8], Philippe Goyette[4], Todd Green[2], Jonas Halfvarson[9], Talin Haritunians[10], Joshua M Korn[2], Finny Kuruvilla[2,11], Caroline Lagacé[4], Benjamin Neale[1,2], Ken Sin Lo[4], Phil Schumm[12], Leif Törkvist[13], National Institute of Diabetes and Digestive Kidney Diseases Inflammatory Bowel Disease Genetics Consortium (NIDDK IBDGC)[14], United Kingdom Inflammatory Bowel Disease Genetics Consortium[14], International Inflammatory Bowel Disease Genetics Consortium[14], Marla C Dubinsky[15], Steven R Brant[16,17], Mark S Silverberg[18], Richard H Duerr[19,20], David Altshuler[1,2], Stacey Gabriel[2], Guillaume Lettre[4], Andre Franke[7], Mauro D'Amato[21], Dermot P B McGovern[10,22], Judy H Cho[6], John D Rioux[4], Ramnik J Xavier[1,2,5] & Mark J Daly[1,2]

nature genetics

Rare variants affect splicing



ESE = exonic splicing enhancer

ESS = exonic splicing silencer

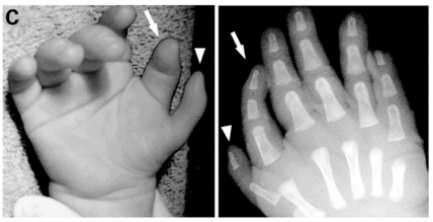
ISE = Intronic splicing enhancer

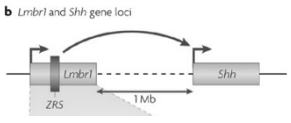
ISS = Intronic splicing silencer

Nature Reviews Genetics 2004 5: 389-396

SHH
reveal single mutations with large effects

Development 2005 132 : 4 797-803



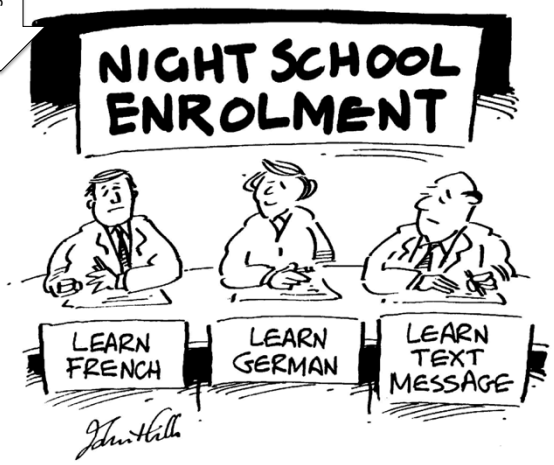


Hemingway cat with six toes

Hum. Mol. Genet. (2008) 17 (7): 978-985

III. Epigenetics

Epigenetic languages of the genome



a. Chromatin

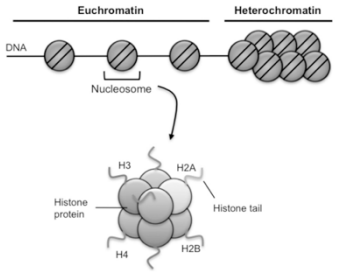
b. Noncoding RNA

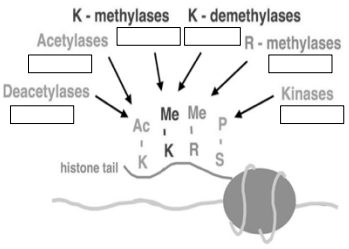
c. Nuclear architecture

d. DNA methylation

a. Chromatin

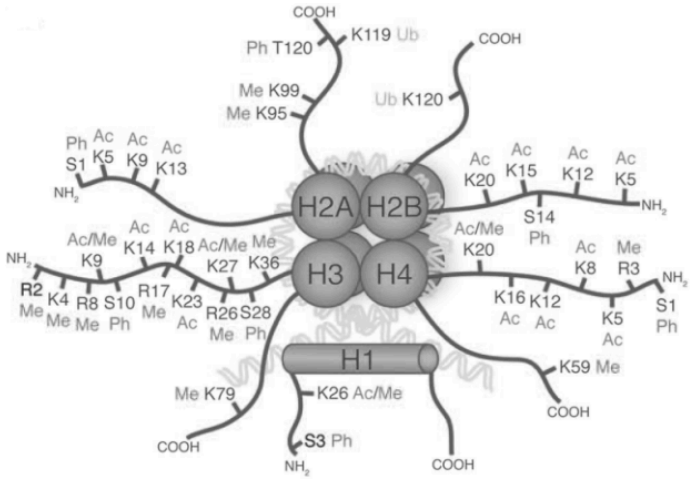
Active and inactive chromatin





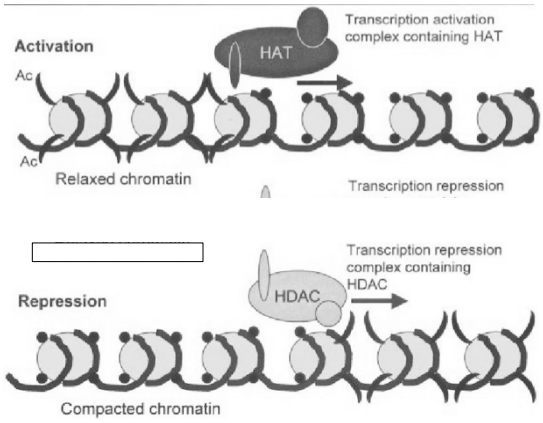
Front. Immunol., 19 December 2012

Locations of histone modifications

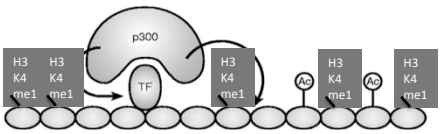


Stem Cells and Epigenetic Reprogramming
Perla Cota, Mehdi Shafa and Derrick E. Rancour

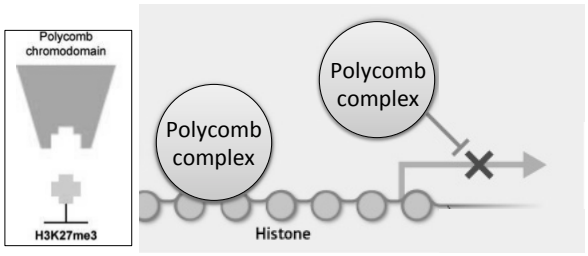
Activation and repression



Regulatory modifications



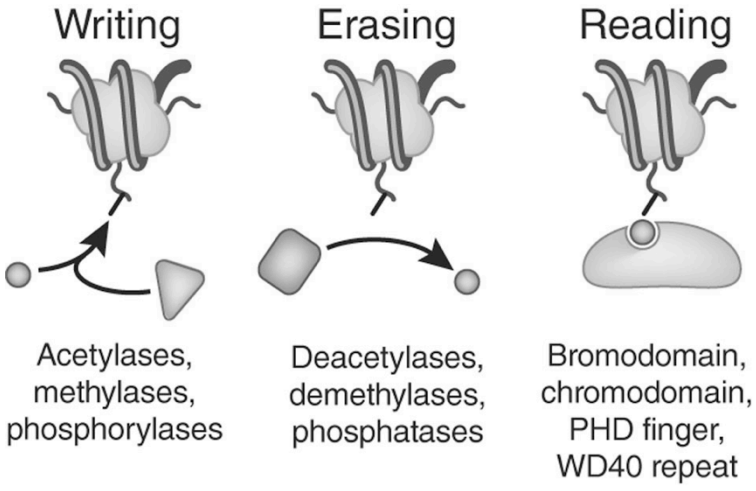
Active enhancer



Repressed promoter

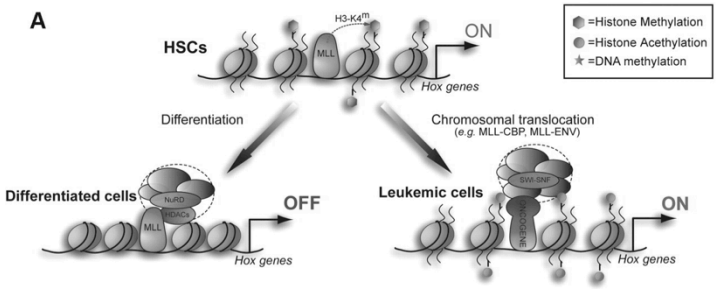
www.rikenresearch.riken.jp/eng/frontline/5514

Chromatin code



Nature Immunology 11, 565–568 (2010)

Leukaemia associated fusion proteins



Di Croce L Hum. Mol. Genet. 2005;14:R77-R84

Human Molecular Genetics

Mutations of epigenome modifiers

Histone variants	*HIST1H1B*
DNA methyltransferases	*DNMT1*
DNA demethylases	*TET2*
Histone acetyltransferases	*EP300*
Histone deacetylases	*HDAC4*
Histone methyltransferases	*MLL*
Histone demethylases	*JARID1C*
Chromatin remodelling factors	*ARID1A*

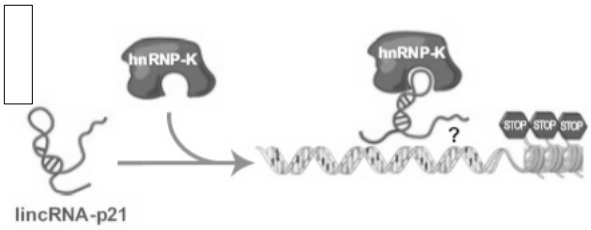
Nature Reviews Cancer 13, 497–510 (2013)

b. Noncoding RNA

Hidden treasures

Noncoding RNA

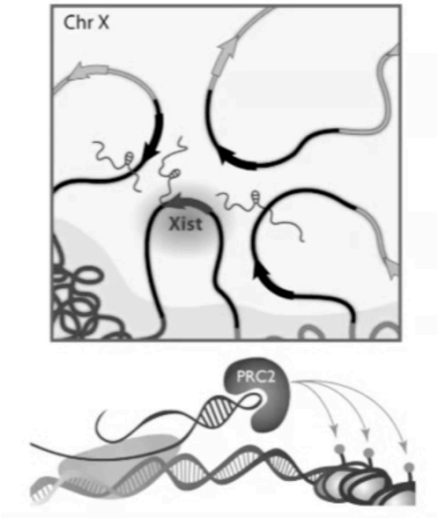
DNA ⟶ RNA ⟶ ~~Protein~~



I.
II.
III.
IV.

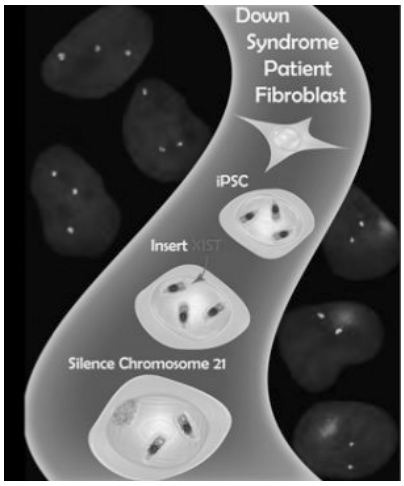
Oncogenic & tumor-suppressor lincRNAs

XIST exploits 3D architecture

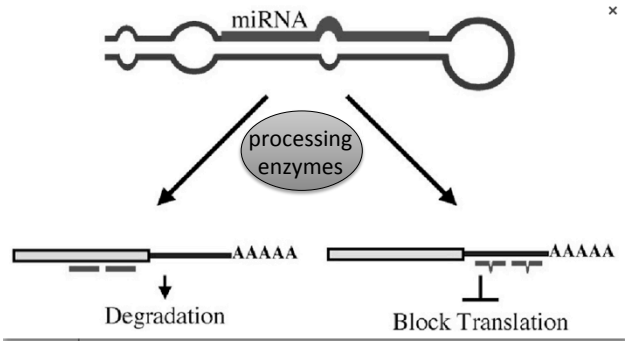


http://www.youtube.com/watch?v=P3X4ujzRxc4#t=150

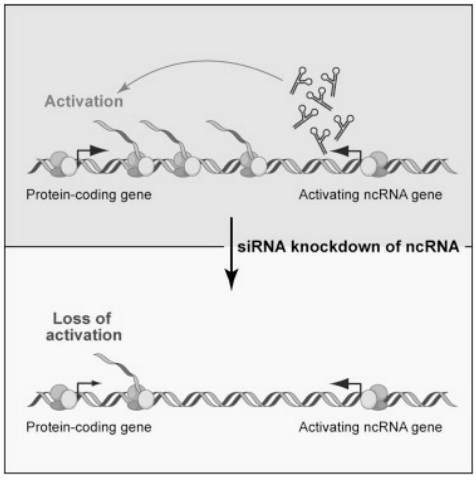
Silencing Down syndrome



MicroRNA



eRNA

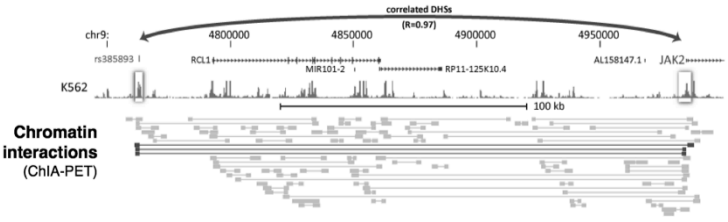


c. Nuclear architecture

Genome architecture

OrganeyezIt

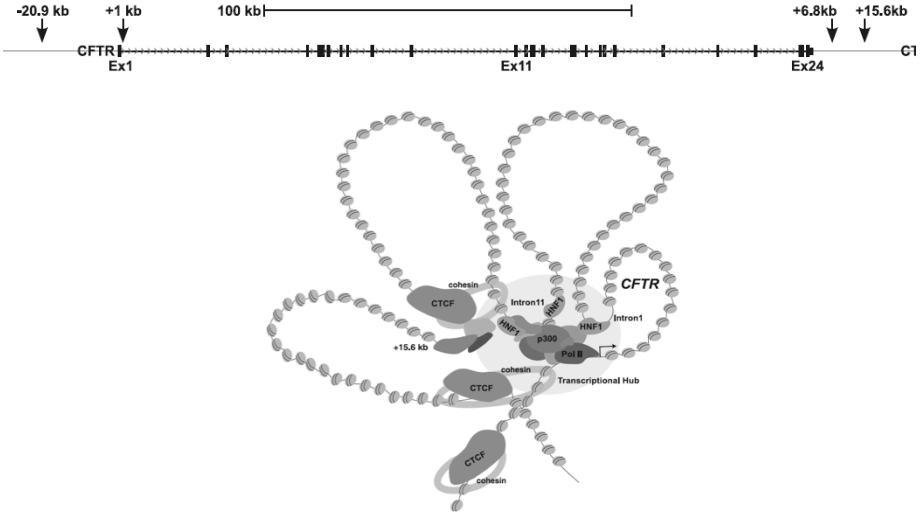
Long distance interactions



Chromatin Interaction Analysis by Paired-End Tag Sequencing (ChIA-PET)

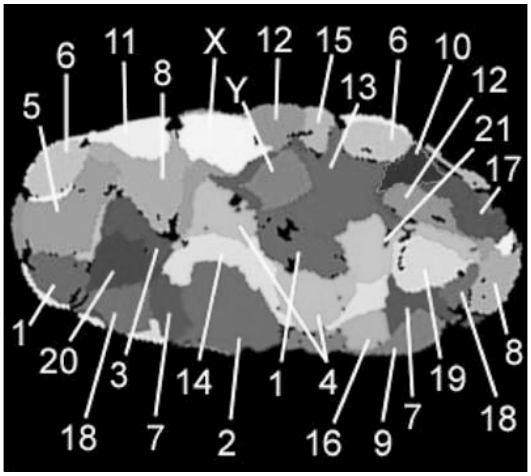
Science 7 September 2012:
Vol. 337 no. 6099 pp. 1190-1195

3D regulatory structures via CTCF



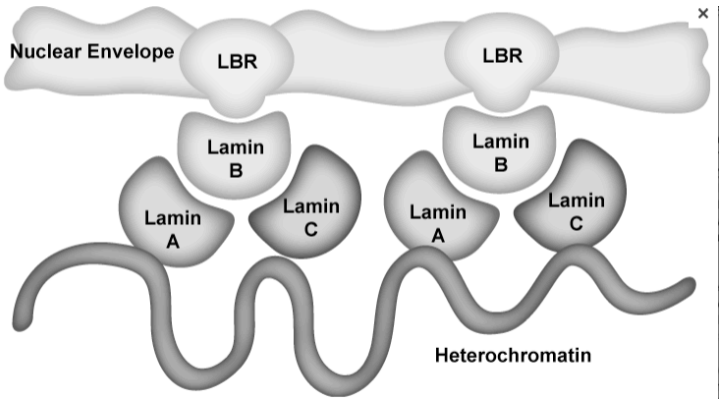
Biochem. Cell Biol. 89: 489–494 (2011)

Chromosome territories



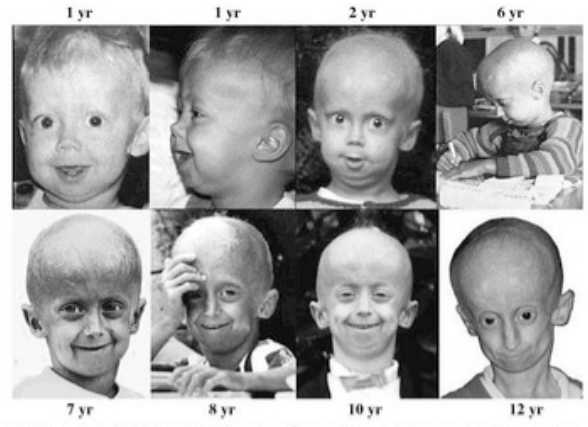
PLoS Biol. 2005 3:e157

Laminar interactions



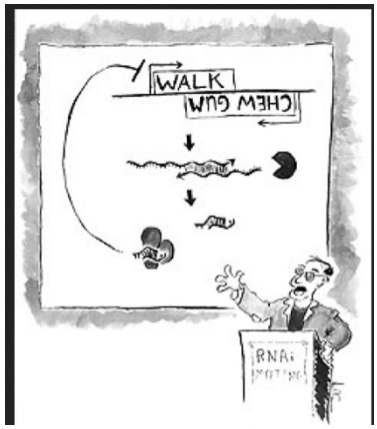
PLoS Biol. 2005 3:e157

Progeria



Am J. Med Genet. 23:2603-24

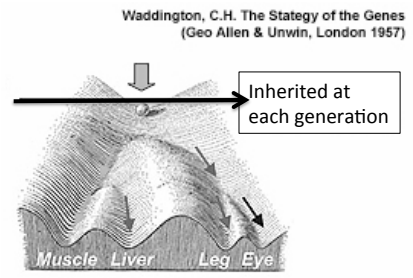
Emerging paradigms

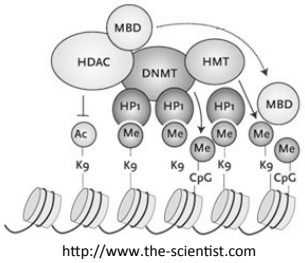


Sean Taverna

d. DNA Methylation

Waddington's epigenetic landscape

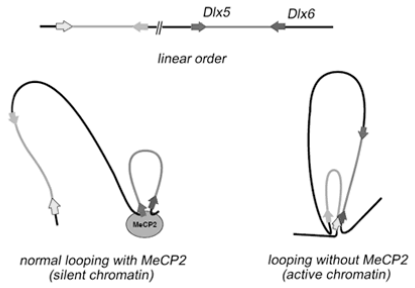




http://www.the-scientist.com

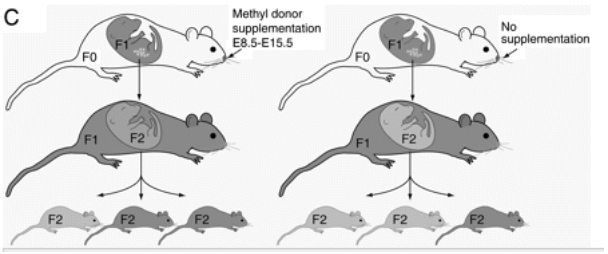
MeCP2 and Rett Syndrome

Rett Syndrome Research Foundation

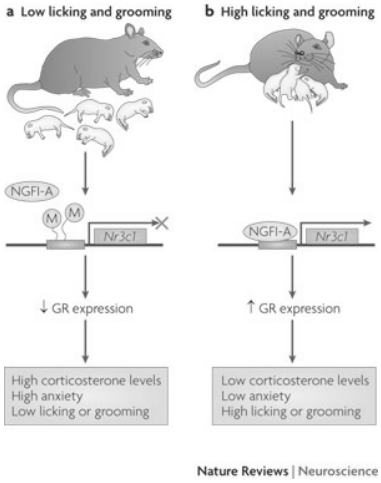


NATURE GENETICS
VOLUME 37 JANUARY 2005

Nutrition



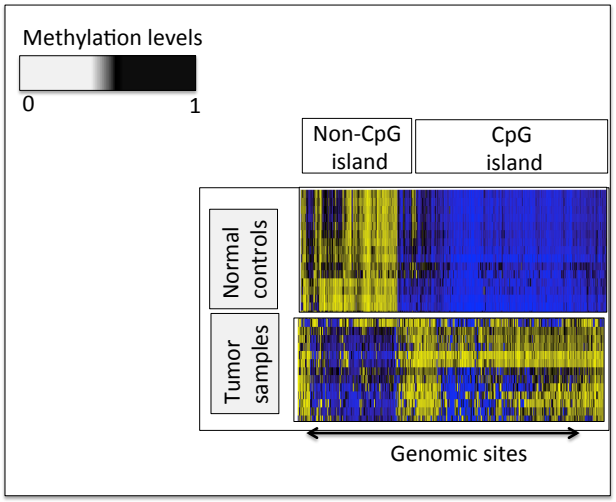
Behavioral traits



Nature Reviews Neuroscience 10, 446-457 (June 2009)

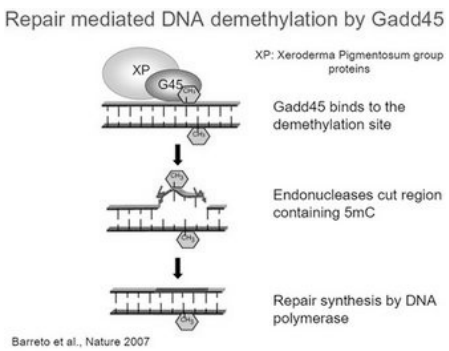
Plausible health interventions

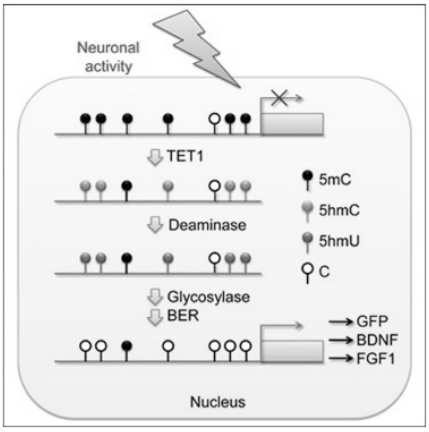
Methylator phenotypes



Kolbe et al. 2012

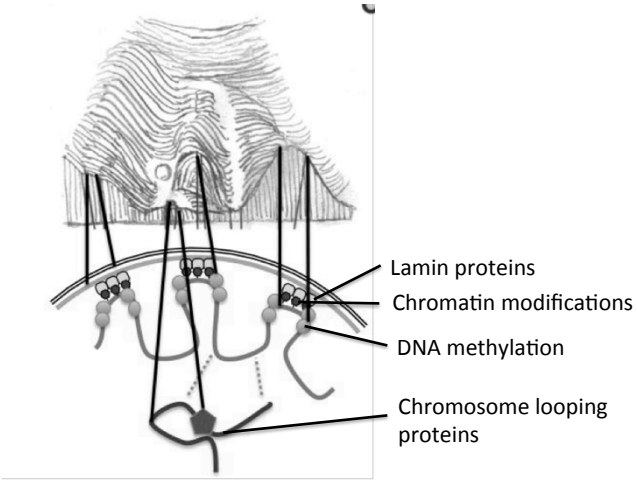
DNA demethylation





Cell, Volume 145, Issue 3, 423-434, 14 April 2011

Dynamic cellular landscapes



Cell. Mar 16, 2012; 148(6): 1123–1131.

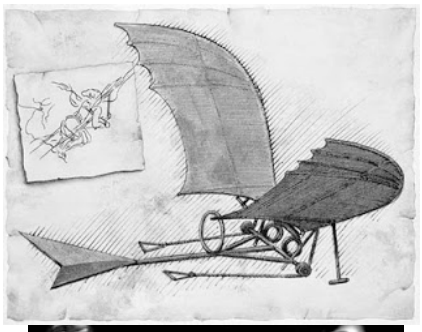
Conclusion

The central dogma has guided decades of research in molecular biology.

Sequencing of the human genome:
- evolutionary diversity among species
- importance of noncoding sequences
- detection of disease processes

Platform for understanding

Knowledge shapes the future



The appropriate Treatment
At the appropriate Dose
For the appropriate Patient
At the appropriate Time
For the appropriate Outcome