FOGA II. WHAT DOES A GENOME HAVE TO DO? - GENOME FUNCTION AND ORGANIZATION

- Cognitive, computational context

- Sophistication of cellular information processing and control regimes

- Functional requirements of information storage organelle in living cell

Molecular Influences on the Genome that are more Informational than Mechanical

- Signaling molecules (hormones, cytokines, second messengers)
- Cell surface receptors for nutrients, signals, surfaces, neighboring cells
- Internal monitors for error & damage repair, checkpoint control
- Signal transduction networks to process information from receptors & monitors (e.g.kinase cascades, cell cycle control circuits)

Genome as Cellular Information Storage Organelle - Functional Requirements

1. Proper physical organization in the nucleoid or nucleus
2. Hold data files for RNA & protein molecules
3. Facilitate data file expression at right time & place
4. Promote DNA replication once per cell cycle
5. Facilitate proper transmission of replicated genome to daughter cells
6. Faciliate replication proofreading and DNA damage repair
7. Permit genome restructuring during the normal life cycle
8. Permit genome restructuring in response to crisis

Without #1 - 7, normal reproduction is not possible; without function #8, evolution is not possible.

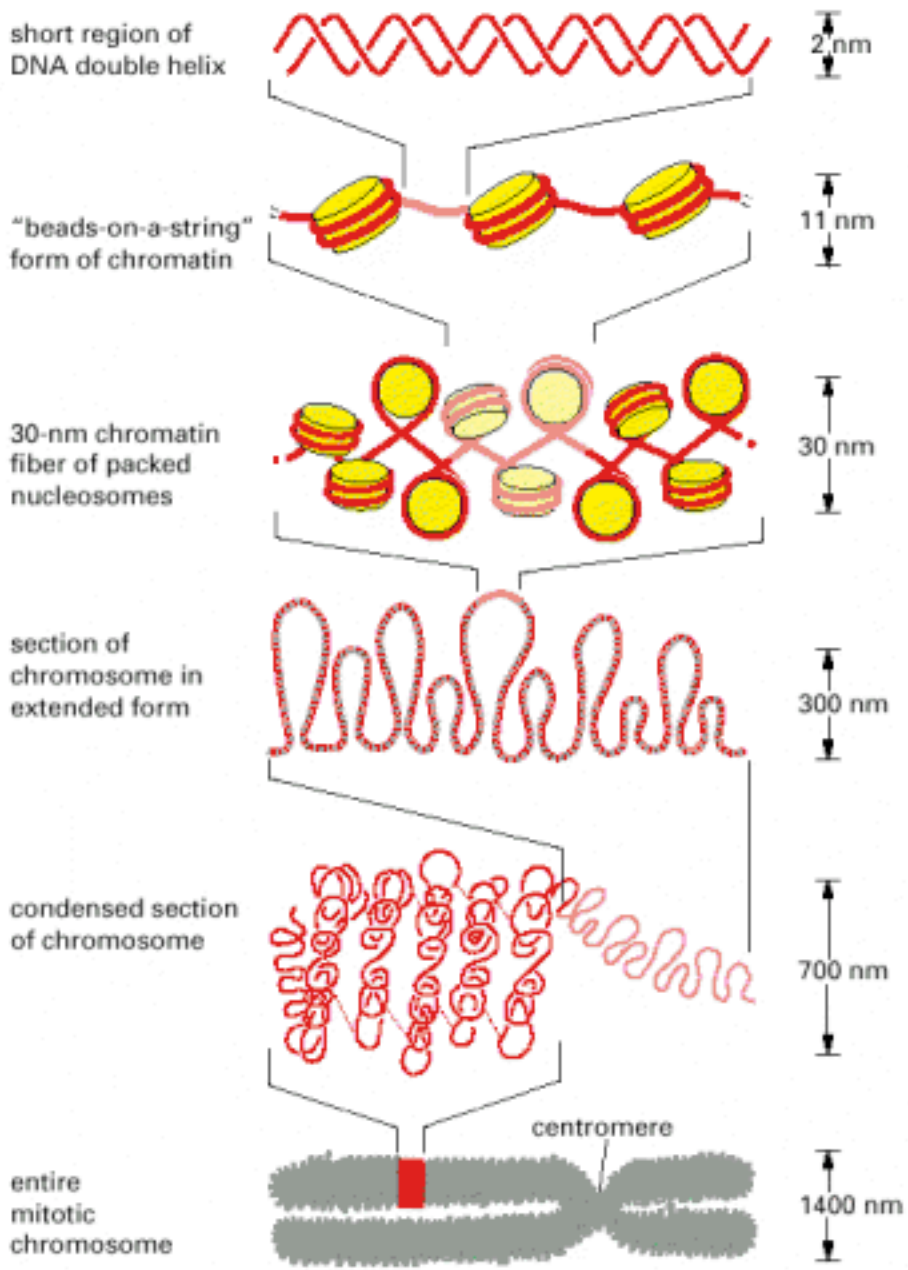
A Fundamental Reality

- In isolation, DNA does not do anything; all genome functions involve nucleoprotein complexes

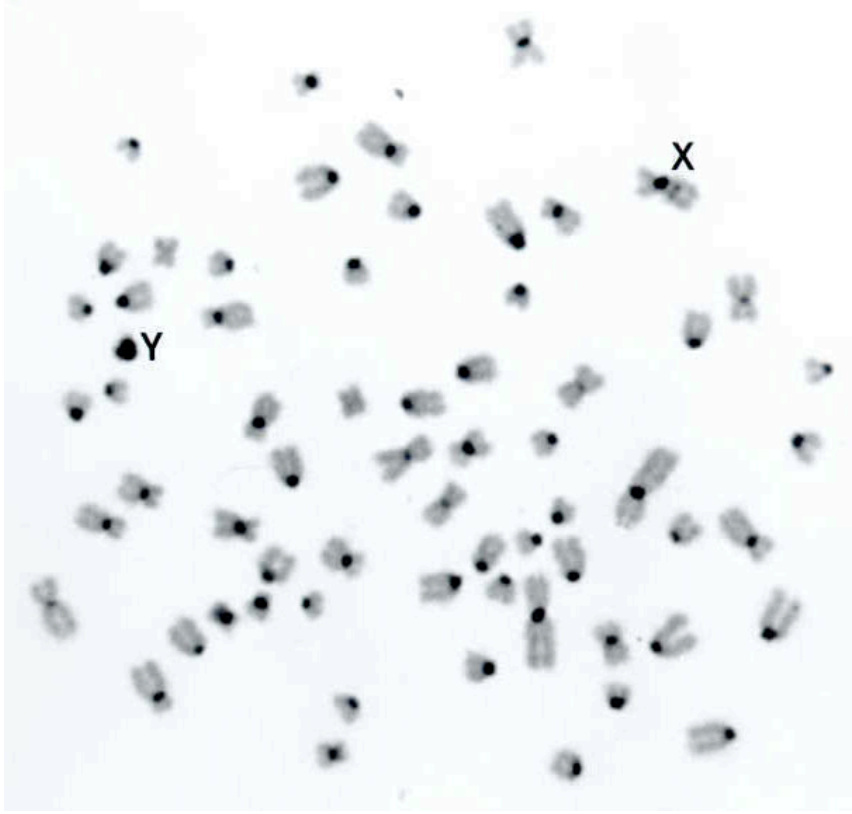
- Consequence 1: all genome activity requires communication with other cellular molecules and compartments

- Consequence 2: Genomic DNA must be formatted by generic signals for proper interaction with other cellular molecules

Physical Organization - Compaction in Euchromatin & Heterochromatin

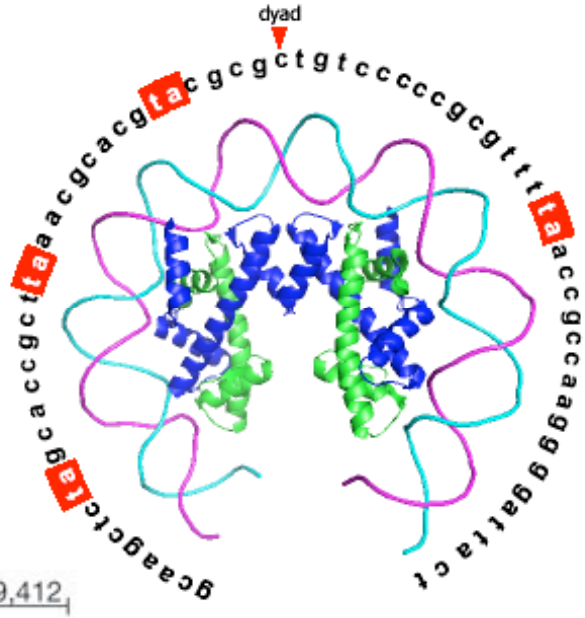


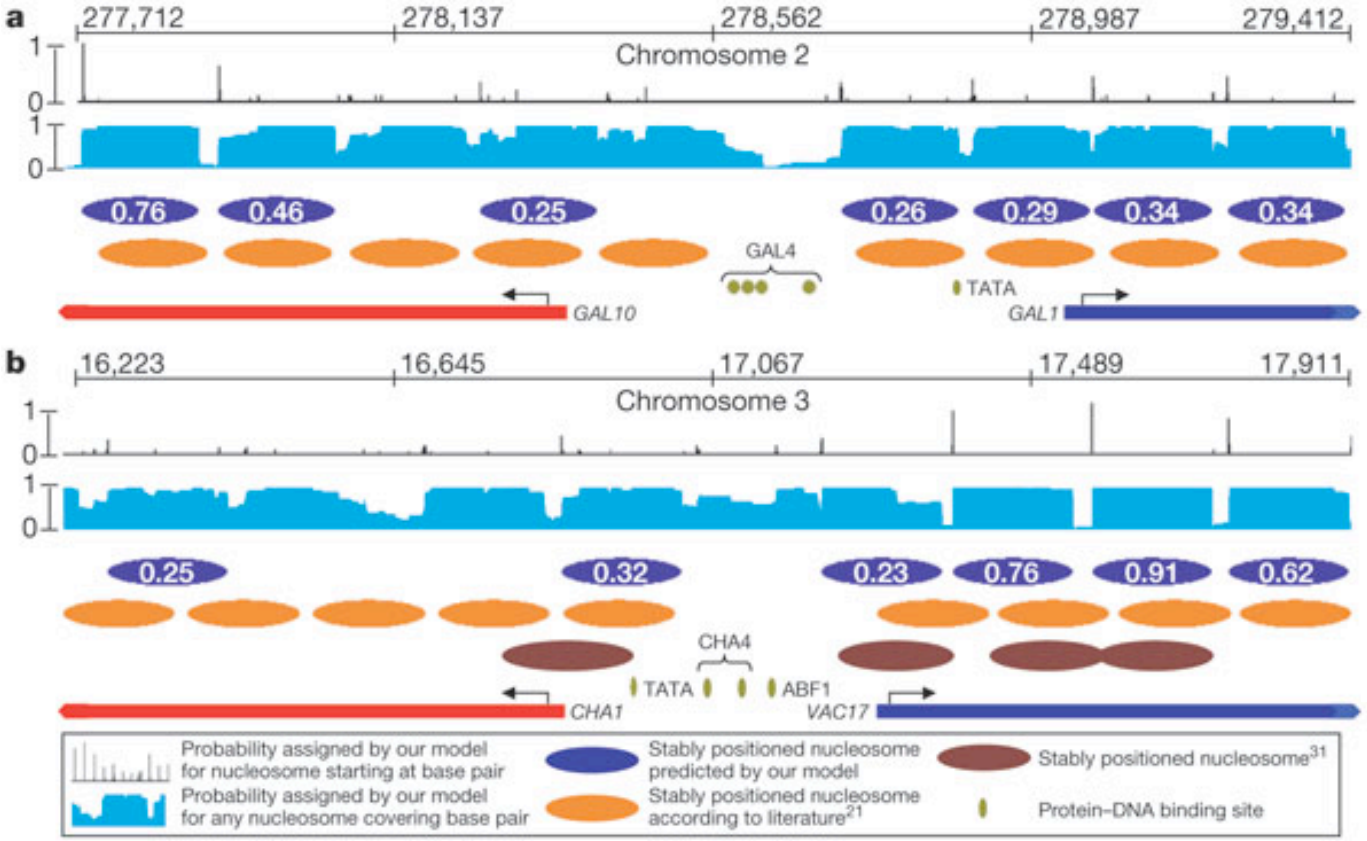
NET RESULT: EACH DNA MOLECULE HAS BEEN PACKAGED INTO A MITOTIC CHROMOSOME THAT IS 10,000-FOLD SHORTER THAN ITS EXTENDED LENGTH



honeybee.helsinki.fi/ users/aulimaki/mare_XY.htm

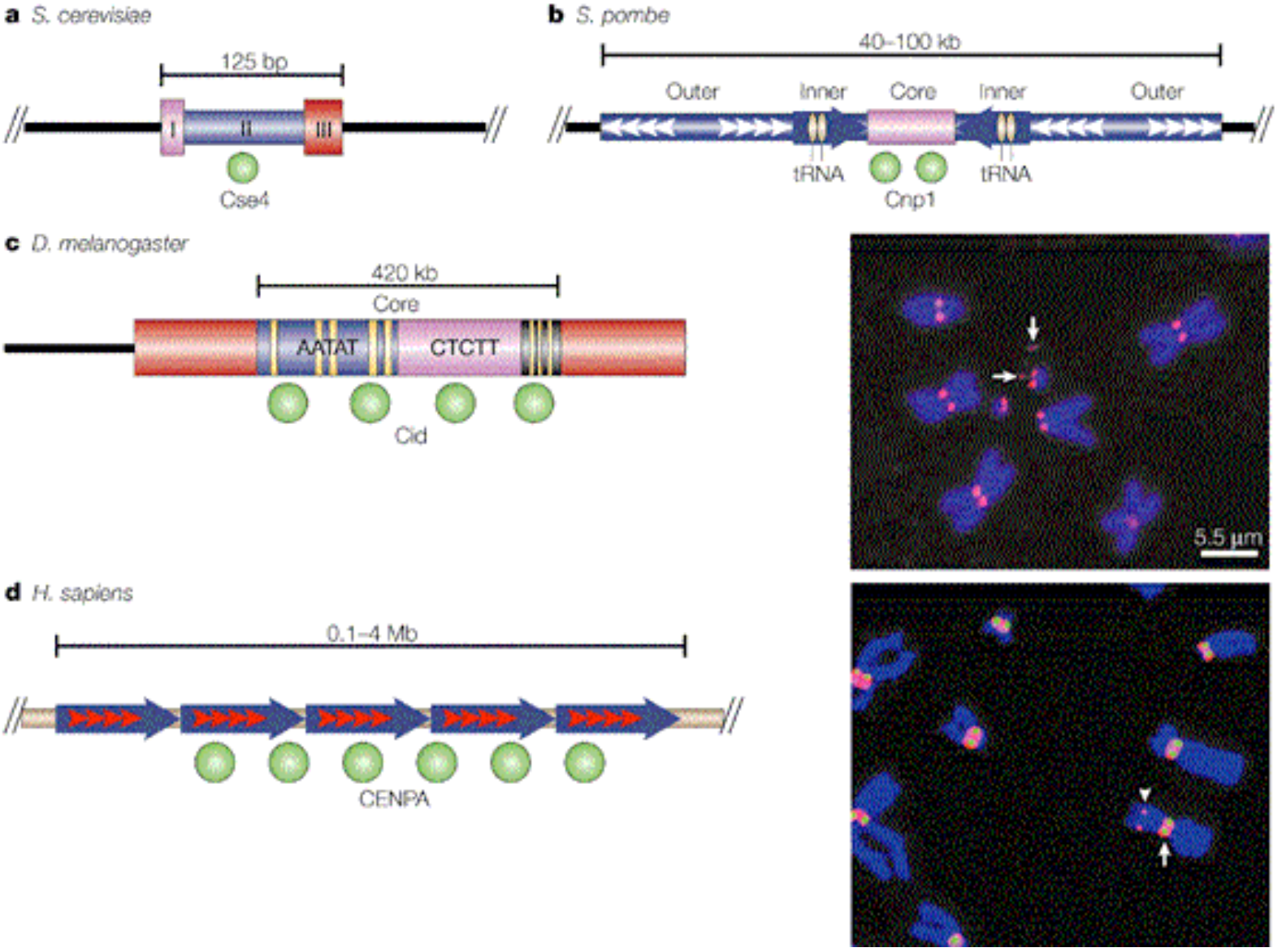
Formatting for Physical Organization - Nucleosome Code





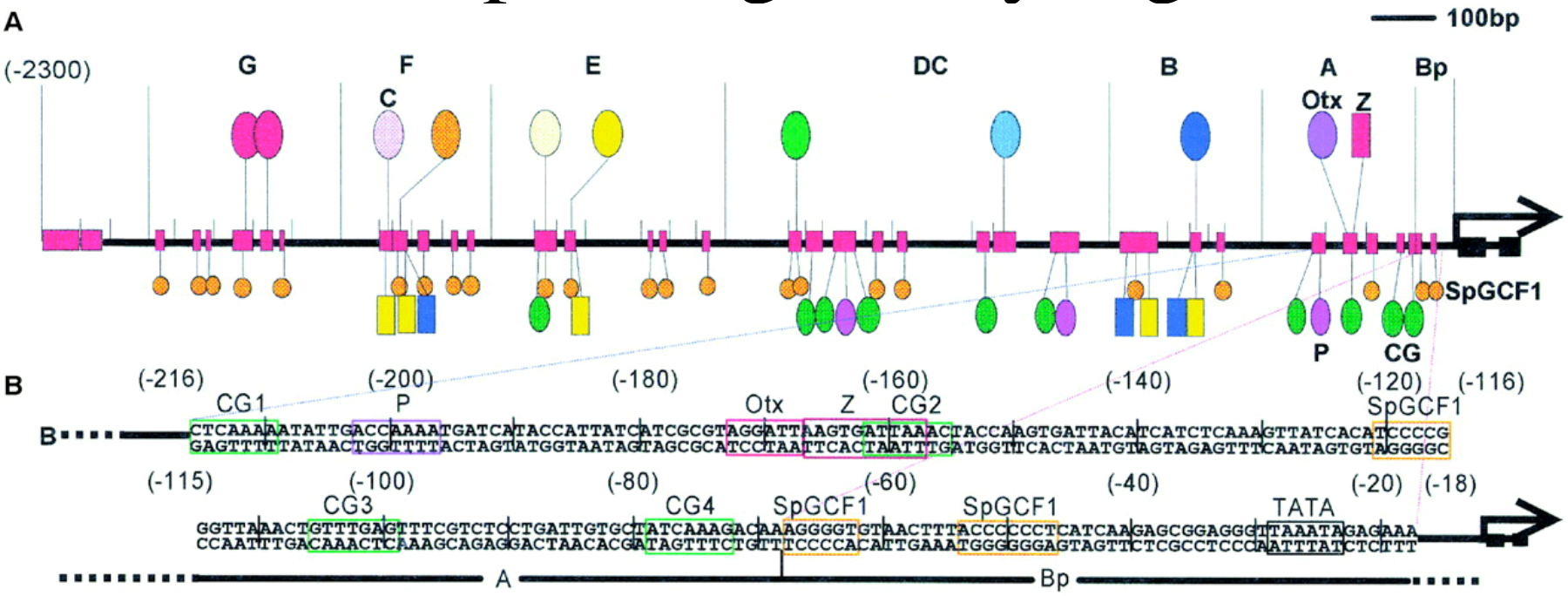
Segal et al. A genomic code for nucleosome positioning. Nature. 2006 Aug 17;442(7104):772-8.

Formatting for chromosome transmission to daughter cells - centromeres



B A Sullivan, M D Blower & G H Karpen DETERMINING CENTROMERE IDENTITY: CYCLICAL STORIES AND FORKING PATHS Nature Reviews Genetics 2; 584-596 (2001)

Formatting for protein synthesis: a complex regulatory region



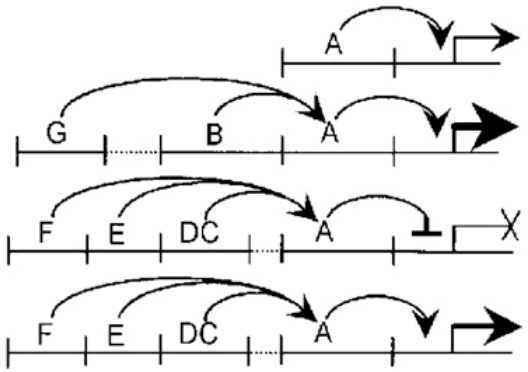
C Module A functions:

Vegetal plate expression in early development:

Synergism with modules B and G enhancing endoderm expression in later development:

Repression in ectoderm (modules E and F) and skeletogenic mesenchyme (module DC):

Modules E, F and DC with LiCl treatment:

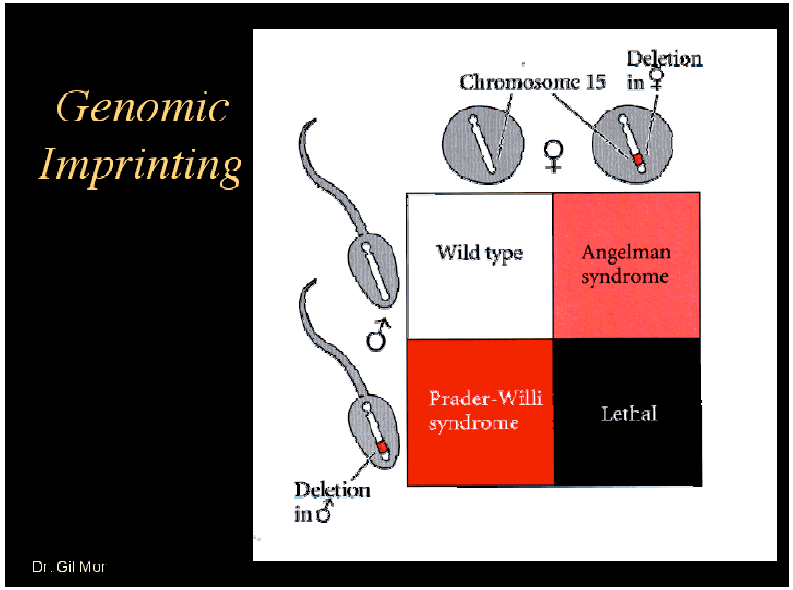


Yuh, C. H., H. Bolouri and E. H. Davidson, 1998 Genomic cis-regulatory logic: experimental and computational analysis of a sea urchin gene, Science **279**: 1896-1902

Genome Information Storage at Three Biological Time Scales

- DNA sequence information: long-term storage over many organismal generations
- Epigenetic storage: large-scale chromatin complexes and DNA modifications heritable over many cell generations
- Computational storage: transient nucleoprotein complexes reflecting the recent history of the cell

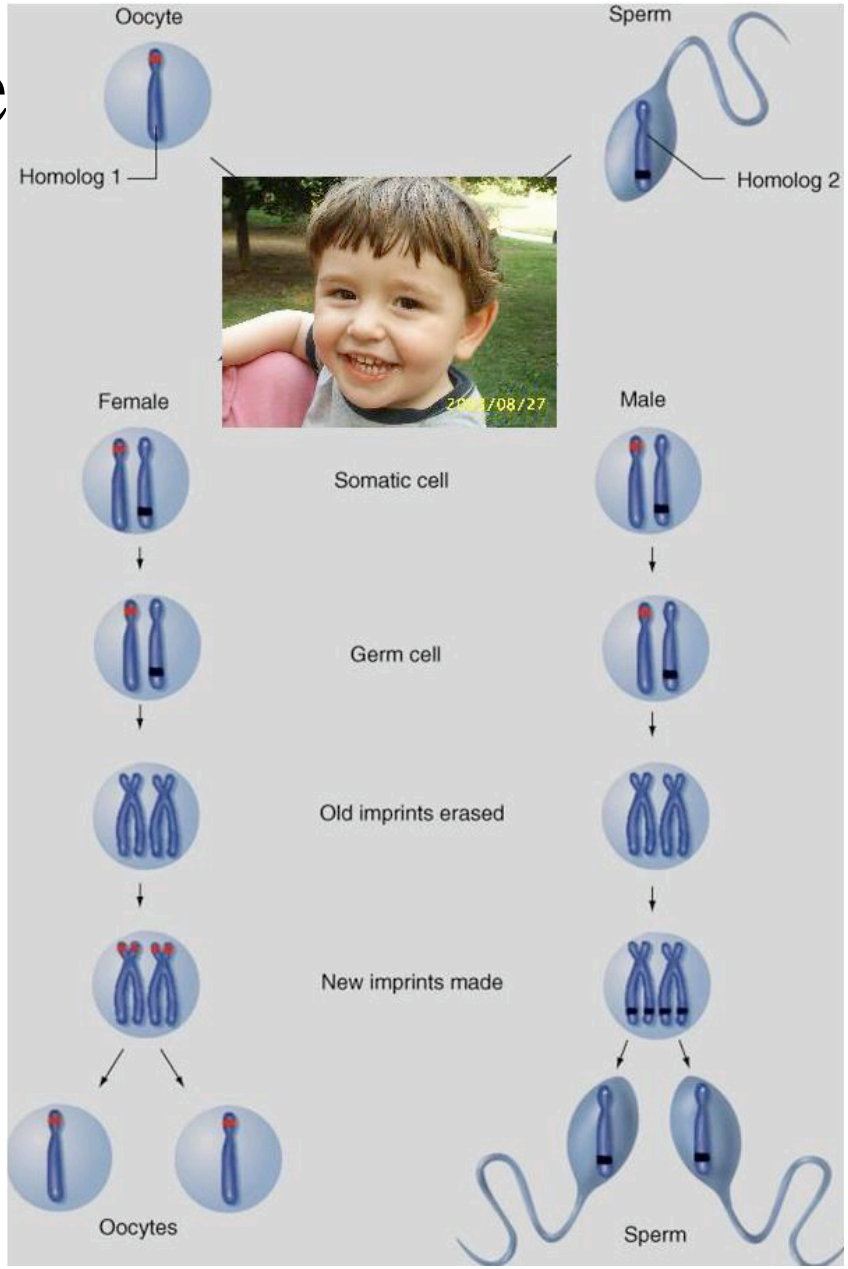
Epigenetic Inheritance - Imprinting



http://www.med.yale.edu/obgyn/reproimmuno/courses/class3/img009.gif

Epigenetic/Imprinted marking:

- Different histone modifications
- Different DNA modifications
- Different chromatin structure (similar to heterochromatin)



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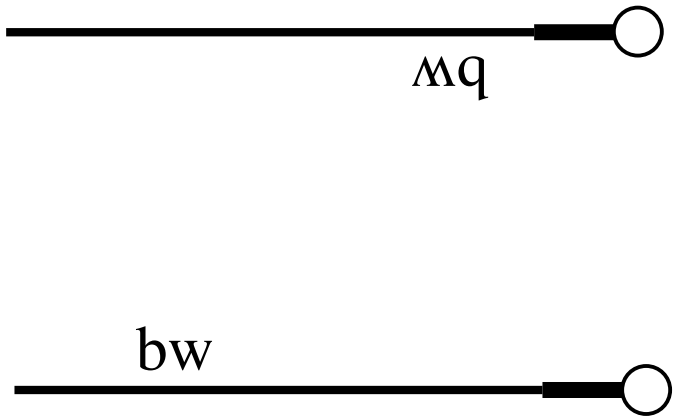
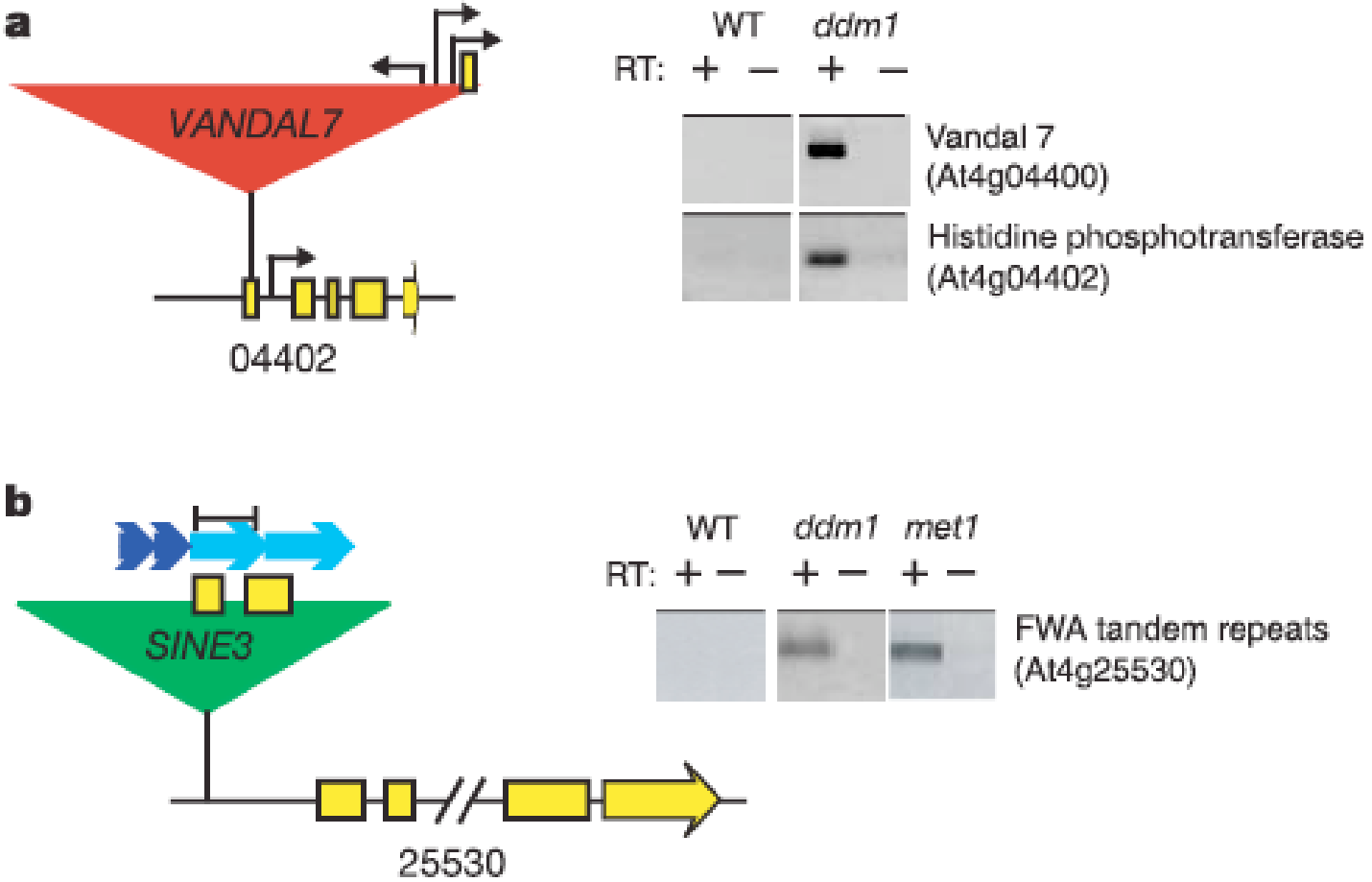
Epigenetic Inheritance - Long-Range Silencing by Heterochromatin



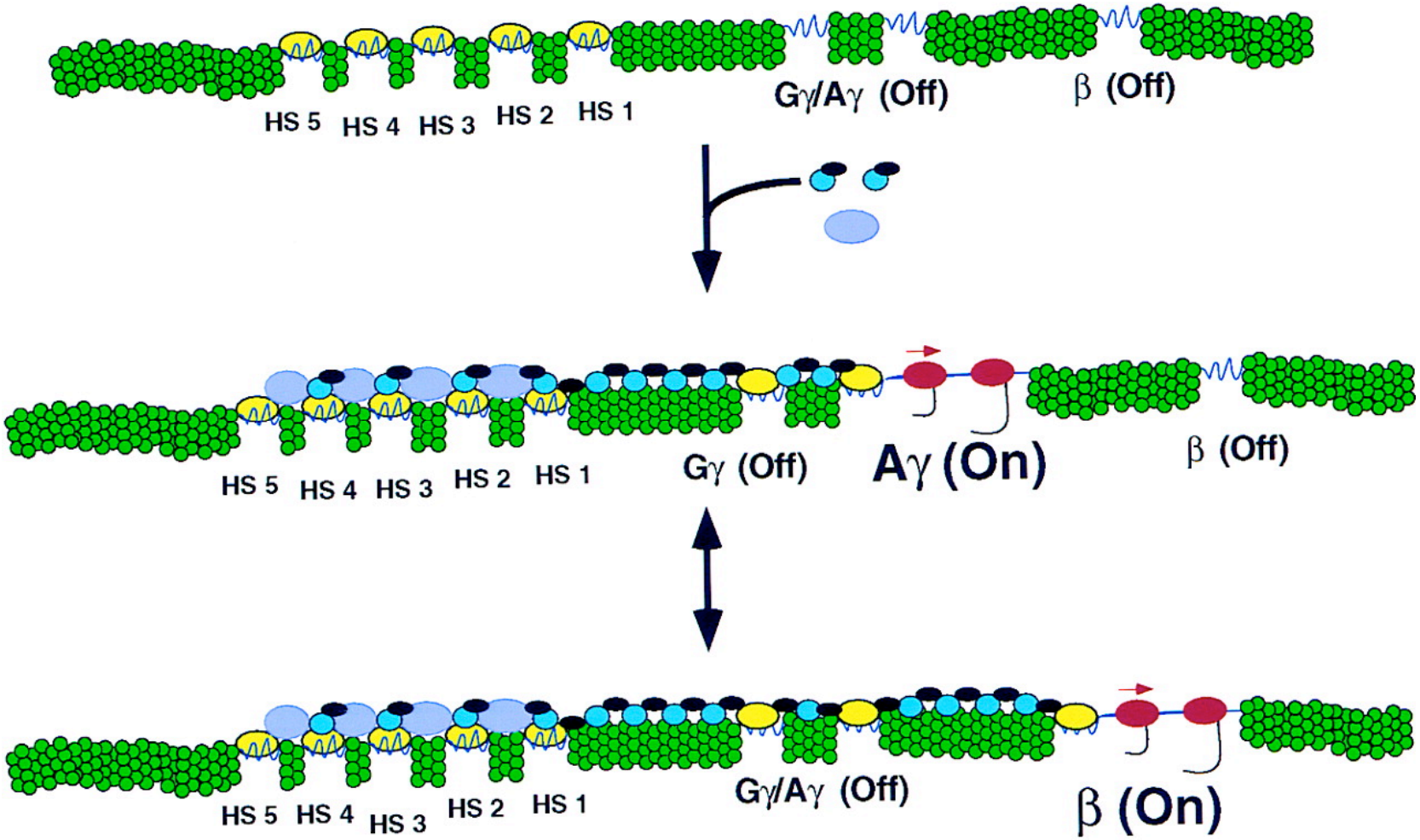
Courtesy of K. Ahmed, Fred Hutchison Cancer Center.

Epigenetic inheritance: silencing (imprinting) by genomic repeats



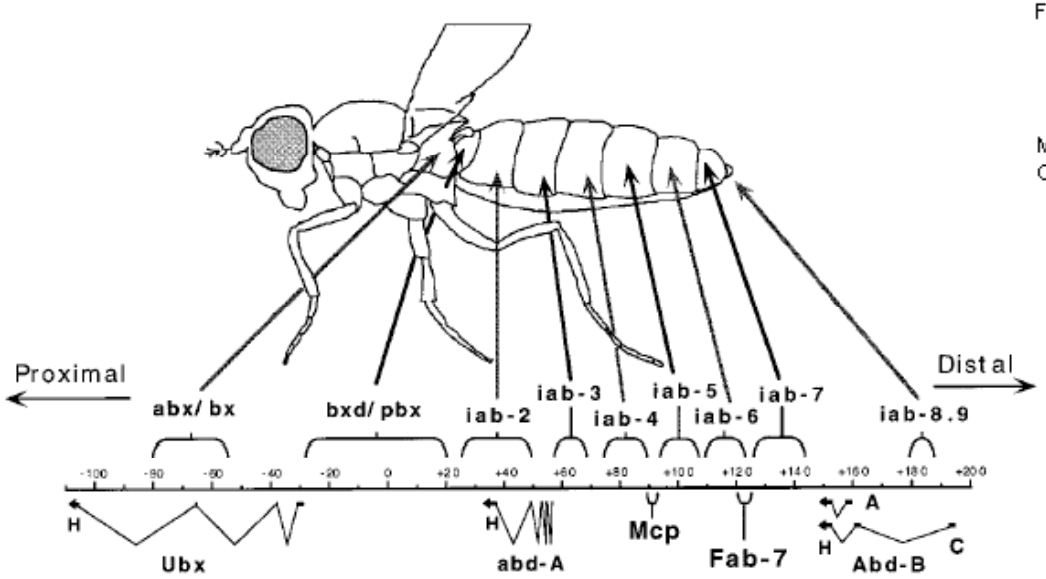
Lippman Z, Gendrel AV, Black M, Vaughn MW, Dedhia N, McCombie WR, Lavine K, Mittal V, May B, Kasschau KD, Carrington JC, Doerge RW, Colot V, Martienssen R. Role of transposable elements in heterochromatin and epigenetic control. Nature. 2004 Jul 22;430(6998):471-6.

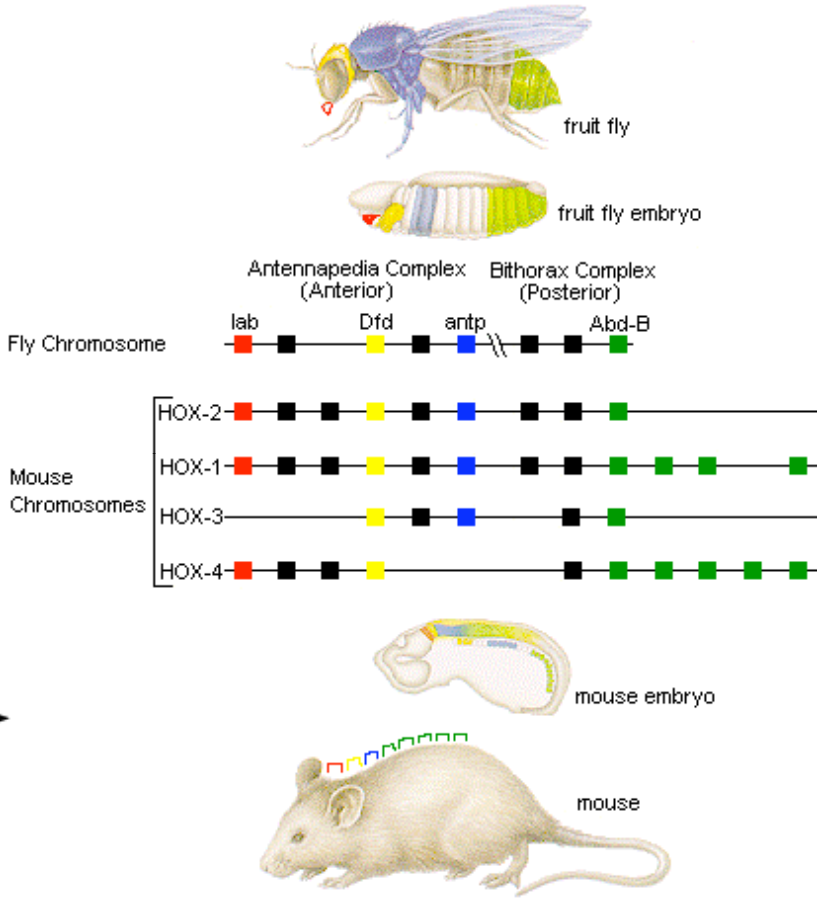
How a complex locus can use epigenetic control in development: the globin switch



M. Bulger and M. Groudine, Looping versus linking: toward a model for long-distance gene activation. Genes Dev 13 (1999), pp. 2465–2477.

A higher-order genomic structure - the Bithorax and Hox complexes



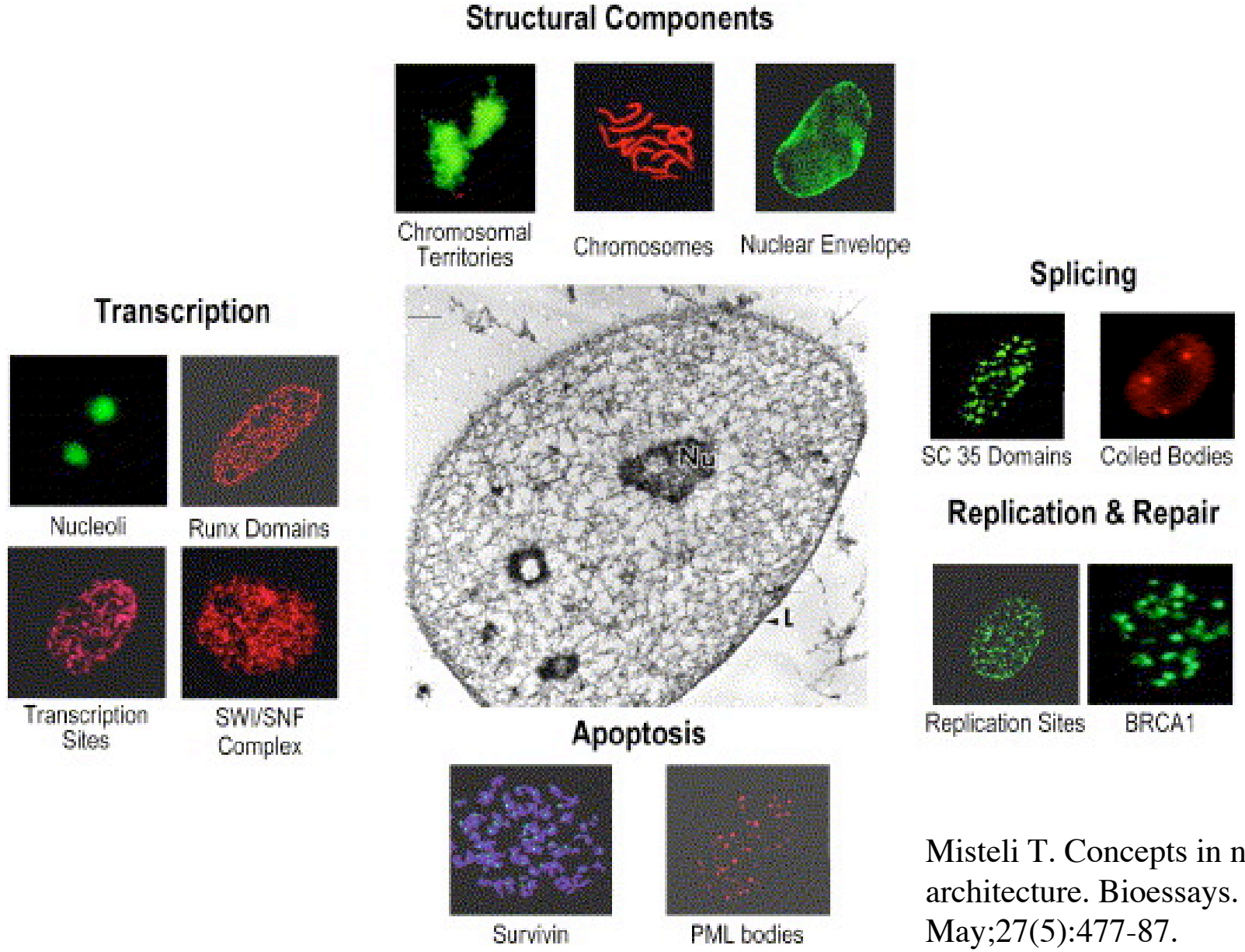


Mihaly J, et al. Chromatin domain boundaries in the Bithorax complex. Cell Mol Life Sci. 1998 54:60-70

Modularity and hierarchy in genomic systems

- proteins composed of domains
- genetic loci composed of regulatory & coding components; specificity from combinatorics
- complex centromeric, telomeric arrays
- complex regulatory systems containing multiple individual loci (globin, Hox complexes)
- chromatin domains integrating large chromosome regions

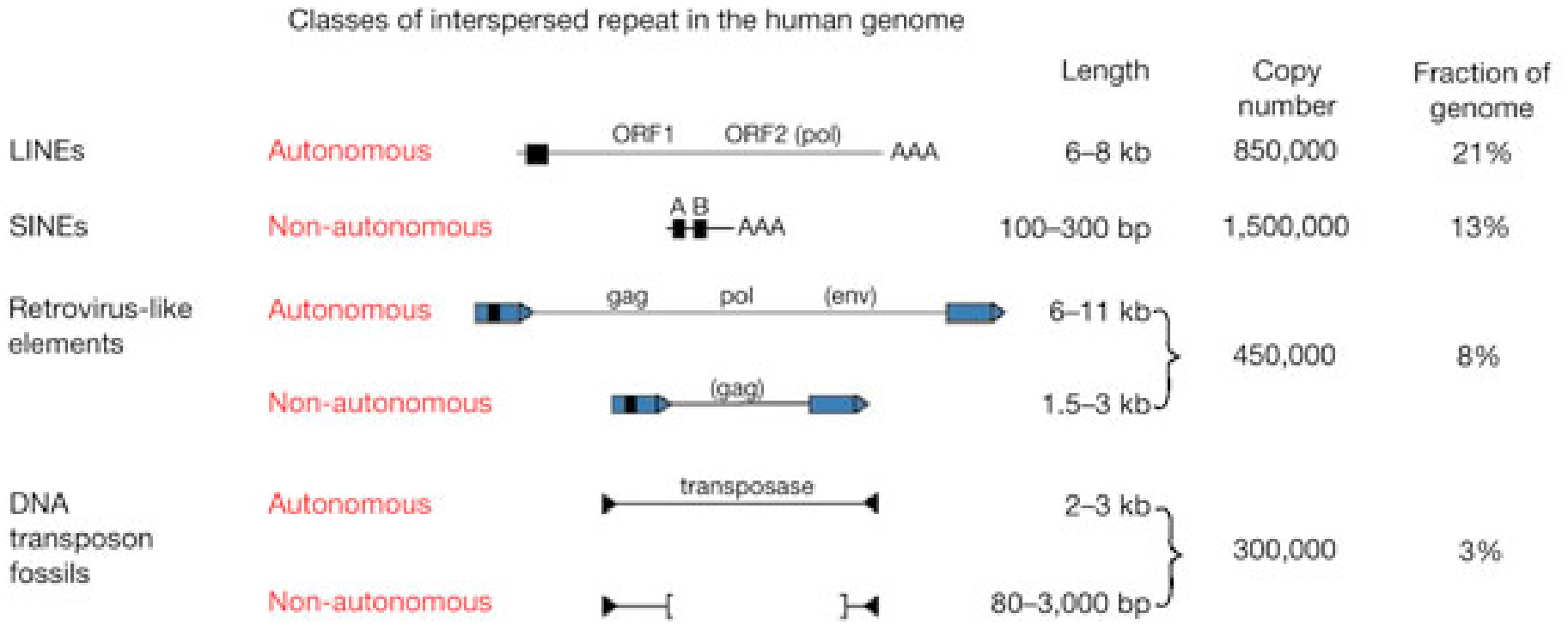
Nuclear Architecture and Genome Function



Misteli T. Concepts in nuclear architecture. Bioessays. 2005 May;27(5):477-87.

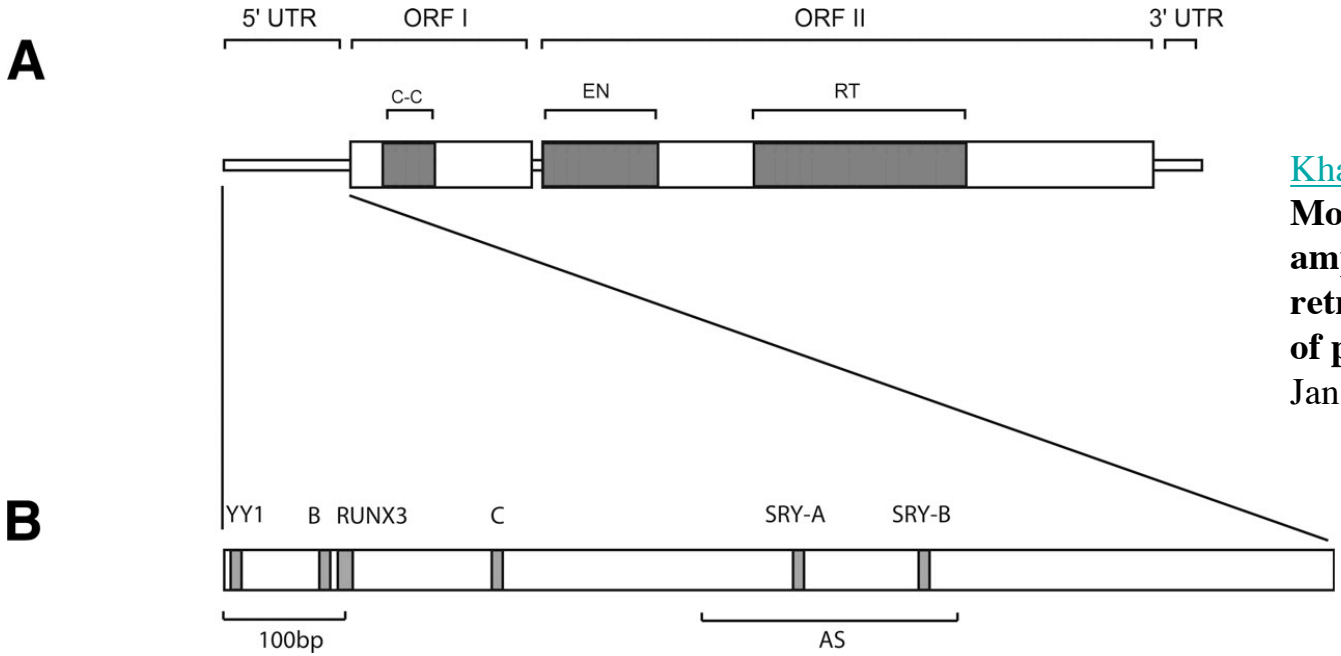
Different sequence element components of the human genome

- coding sequences (data files): ~1.5 - 2% of human genome
- intervening sequences
- repetitive sequences: > 50% of human genome



International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature 409, 860 - 921 (2001)

LINE elements as informatic casettes



Khan H, **Smit A**, **Boissinot S**. **Molecular evolution and tempo of amplification of human LINE-1 retrotransposons since the origin of primates.** Genome Res. 2006 Jan;16(1):78-87.

Documented functions of LINE-1 elements:

- contain sense & anti-sense promoters
- transcriptional enhancer activity
- retard transcript elongation
- 39% of human S/MARs are LINE-1 elements
- imprinting & mono-allelic expression

Shapiro JA and Sternberg Rv. 2005. Why repetitive DNA is essential to genome function. Biol. Revs. **80**, 227-50

Genomes as RW storage systems

- Short-term: restructuring of transcriptional regulatory and other functional complexes during the cell cycle

- Intermediate term: Epigenetic imprinting & erasure of imprints; chromatin reformatting complexes to alter genome function over multiple cell cycles

- Long-term: Natural genetic engineering toolbox for cells to restructure DNA molecules

Genome System Architecture (independent of coding sequence content)

- Use of particular formatting sequences for genome functions
- Organization of special DNA structures (centromeres, telomeres, nucleolar organizing region, higher-level control complexes)
- Identity and location of dispersed repeats throughout the genome
- Organization of genetic loci along chromosomes and positioning with respect to special structures