Oncology for Scientists

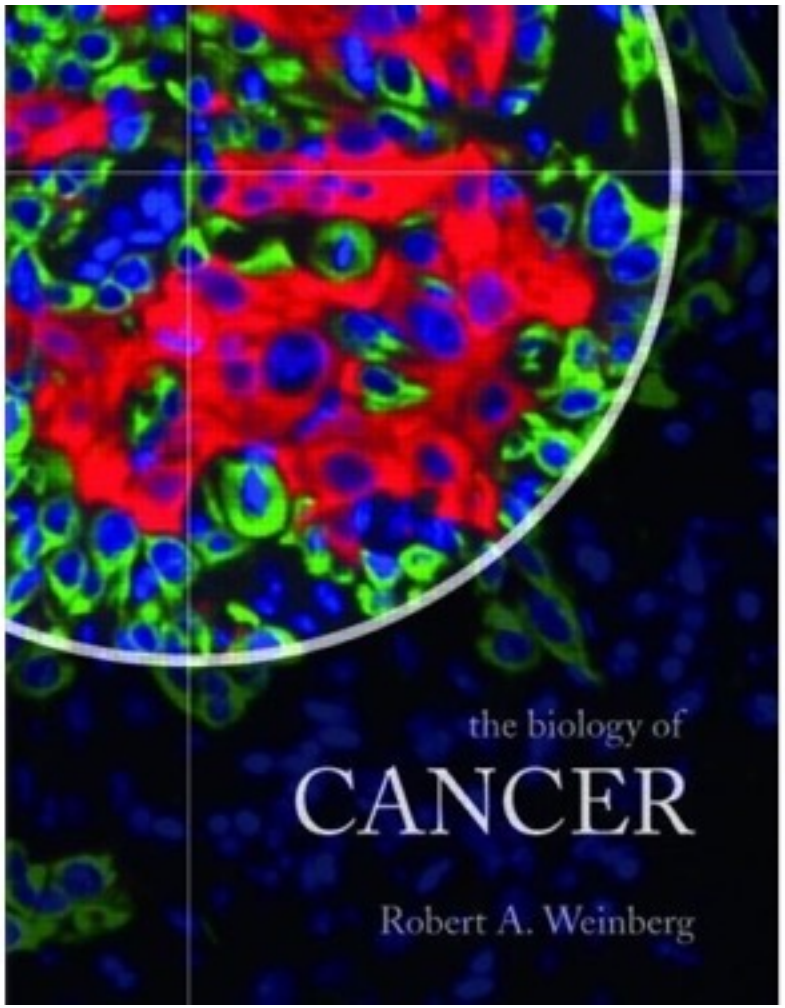
- CHROMOSOME STRUCTURE, REPLICATION, TRANSCRIPTION, TRANSLATION -

Sebastiano Battaglia, PhD
Dept. Pharmacology and Therapeutics
Roswell Park Cancer Institute

Reference books

"The Biology of Cancer"
(Robert Weinberg)

+ online references…



DOGMA IN GENETICS

Let’s brake it down…

Image from: http://www.lhsc.on.ca/Patients_Families_Visitors/Genetics/Inherited_Metabolic/Mitochondria/DiseasesattheMolecularLevel.htm

- Pt. 0 – DNA
- Pt. 1 – DNA replication
- Pt. 2 – DNA transcribed into RNA
- Pt. 3 – RNA translated into proteins

PART 0

DNA

DNA STRUCTURE

- DNA is a macromolecule
- Double helix
- Four nucleotides covalently bond
  - A=T
  - C≡G

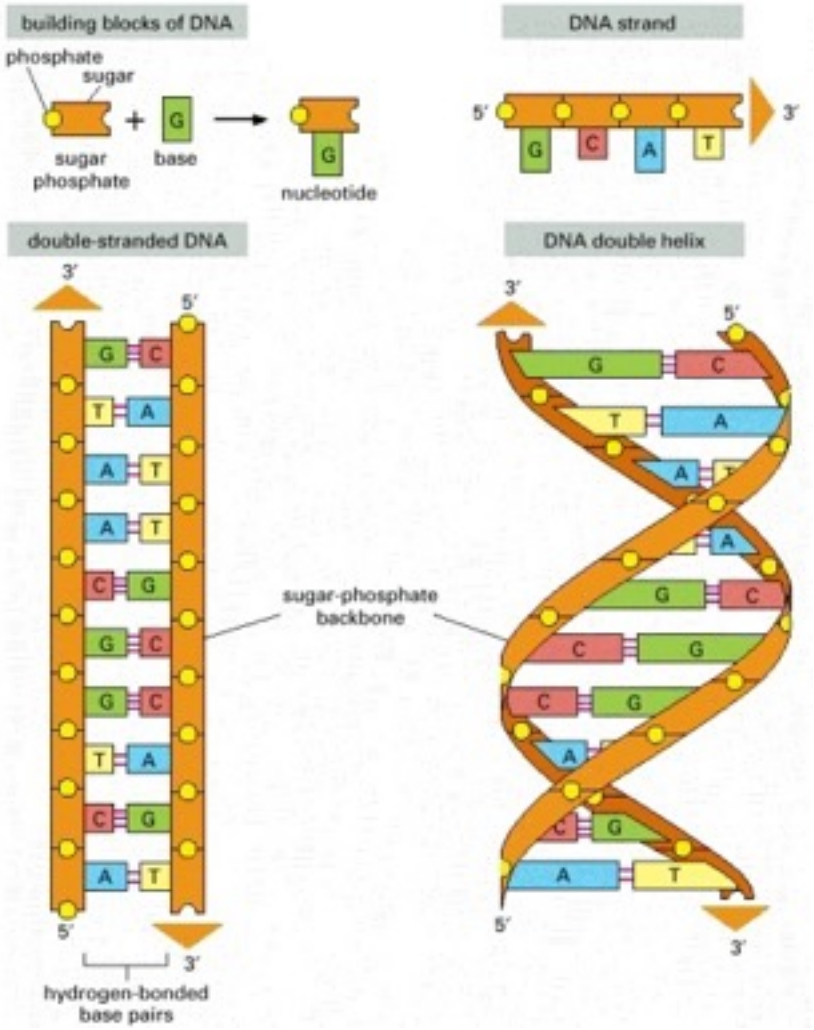
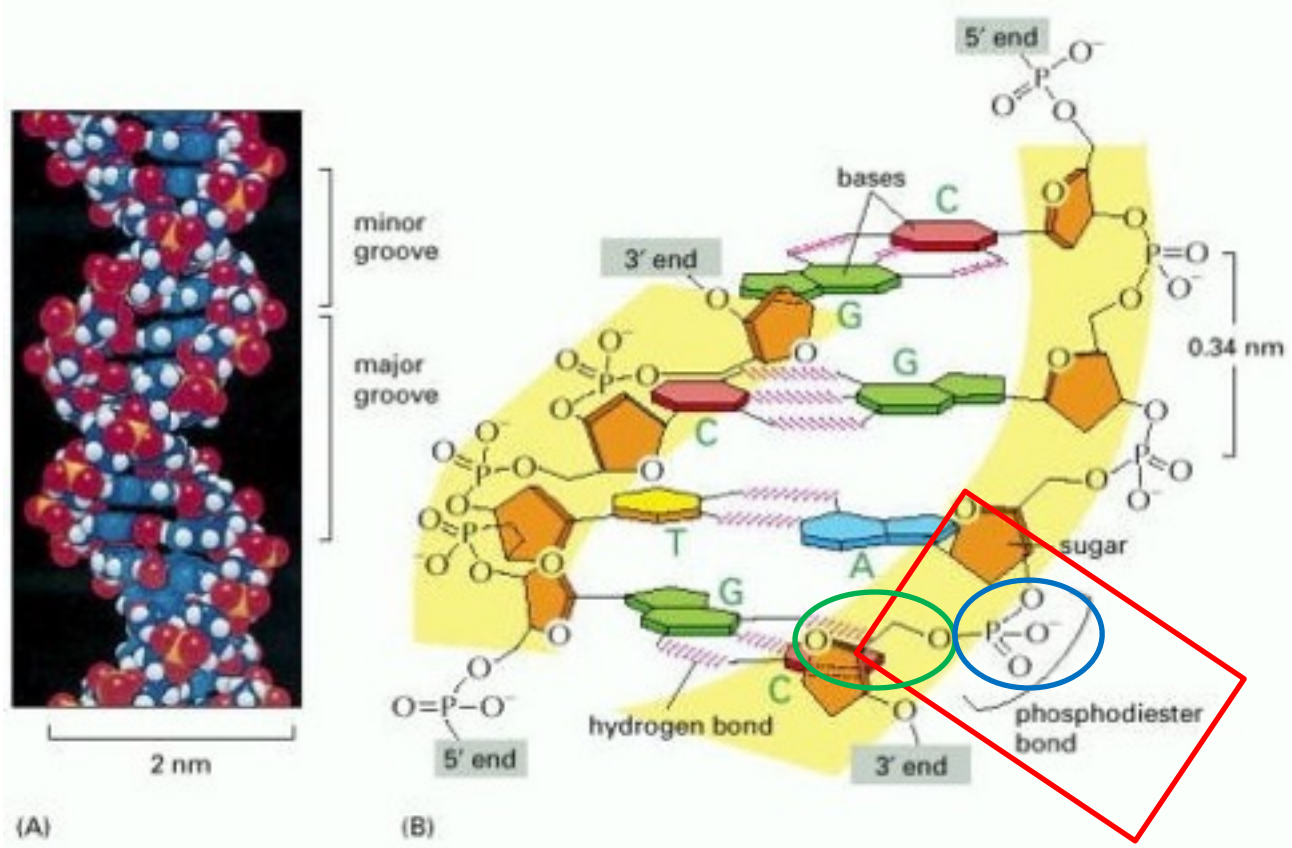
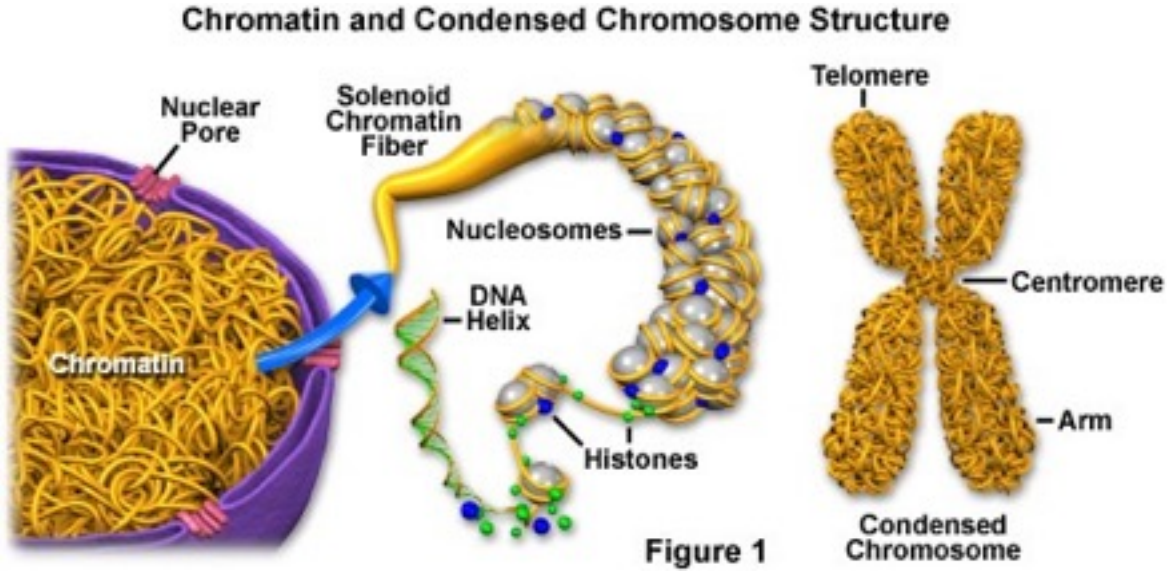


Image from
Molecular Biology of the Cell. 4th edition.
Alberts B, Johnson A, Lewis J, et al.
New York: Garland Science; 2002.



- ~ 2nm diameter
- Phosphodiester bonds between nucleotides on the same strand between 3’-Hydroxil (OH) group on one sugar and the 5’-phosphate (P) on the next one

Image from
Molecular Biology of the Cell. 4th edition.
Alberts B, Johnson A, Lewis J, et al.
New York: Garland Science; 2002.



DNA is packed into chromatin with the help of HISTONE PROTEINS

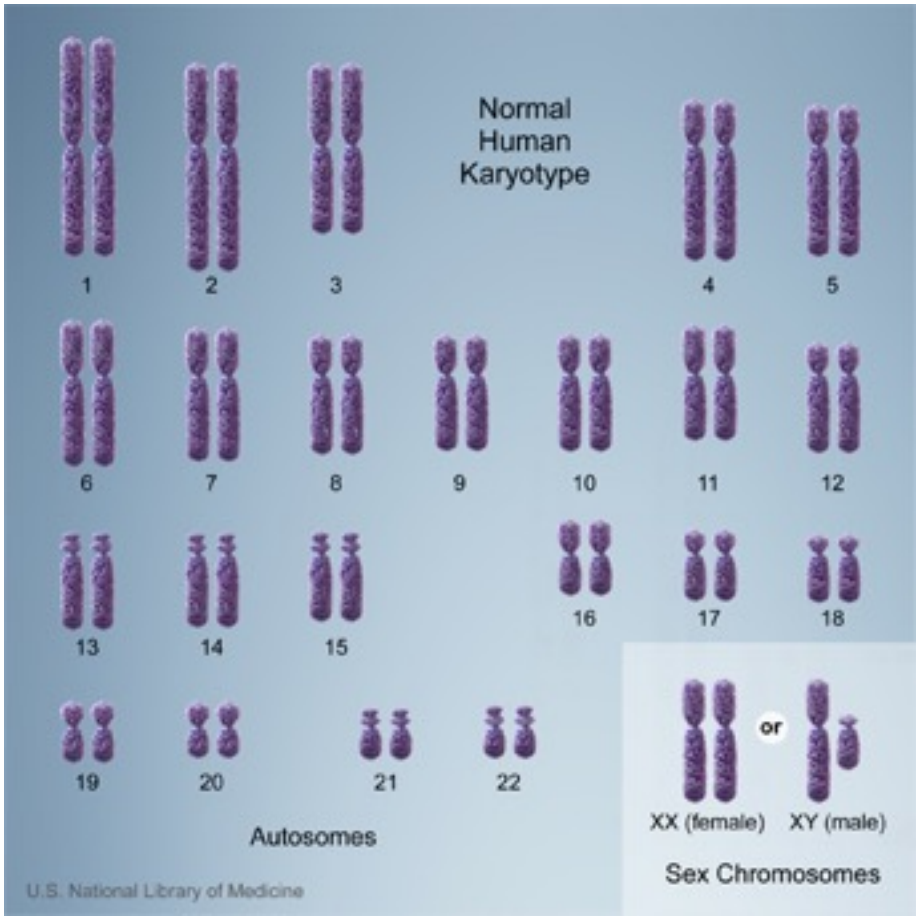
Euchromatin - DNA transcriptionally active

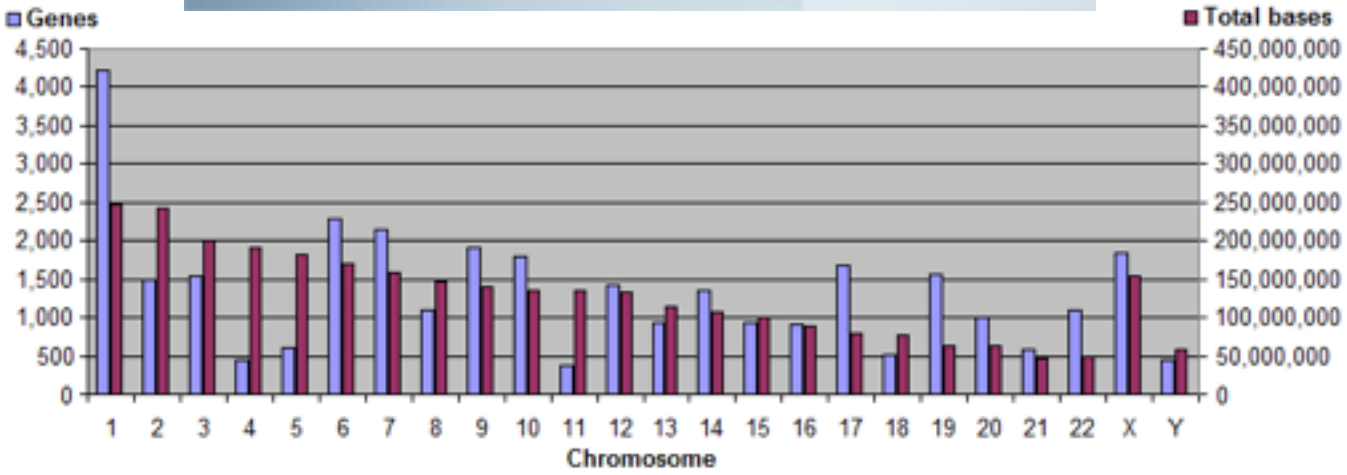
Heterochromatin – very dense DNA, transcriptionally inactive.

Constitutive heterochromatin - never active (around the centromere)

Facultative heterochromatin – active during some portions of the cell cycle

Image from http://micro.magnet.fsu.edu/cells/nucleus/chromatin.html


Normal
Human
Karyotype
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Autosomes
or
XX (female)
XY (male)
Sex Chromosomes
U.S. National Library of Medicine


Genes
Total bases
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
450,000,000
400,000,000
350,000,000
300,000,000
250,000,000
200,000,000
150,000,000
100,000,000
50,000,000
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y
Chromosome

Interesting facts about DNA

1) (length of 1 bp)(number of bp per cell)(number of cells in the body)

$(0.34 \times 10^{-9}\ \text{m})(6 \times 10^{9})(10^{13})$

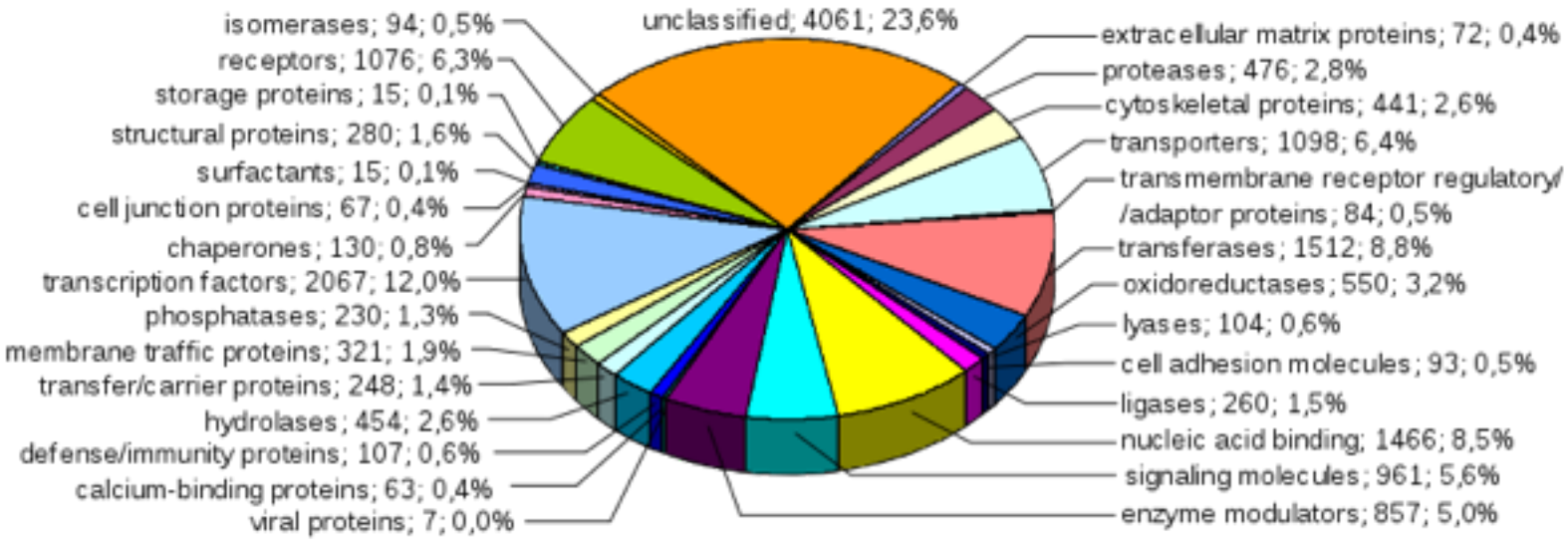
$$2.0 \times 10^{13}\ \text{meters}$$

That is the equivalent of nearly **70 trips from the earth to the sun and back.** On the average, a single human chromosome consists of DNA Molecule that is almost 5 centimeters.

2) It would take a person typing 60 words per minute, eight hours a day, around 50 years to type the human genome.

http://hypertextbook.com/facts/1998/StevenChen.shtml

- ~2.9 billions of base pairs
- ~30k genes



http://en.wikipedia.org/wiki/File:Human_genome_by_functions.svg

TELOMERES

- Telomeres are “caps” at the end of the chromosome formed by repetitive DNA sequences that
  - Prevent fusions of chromosomes with each others
  - Stabilize chromosomes structures

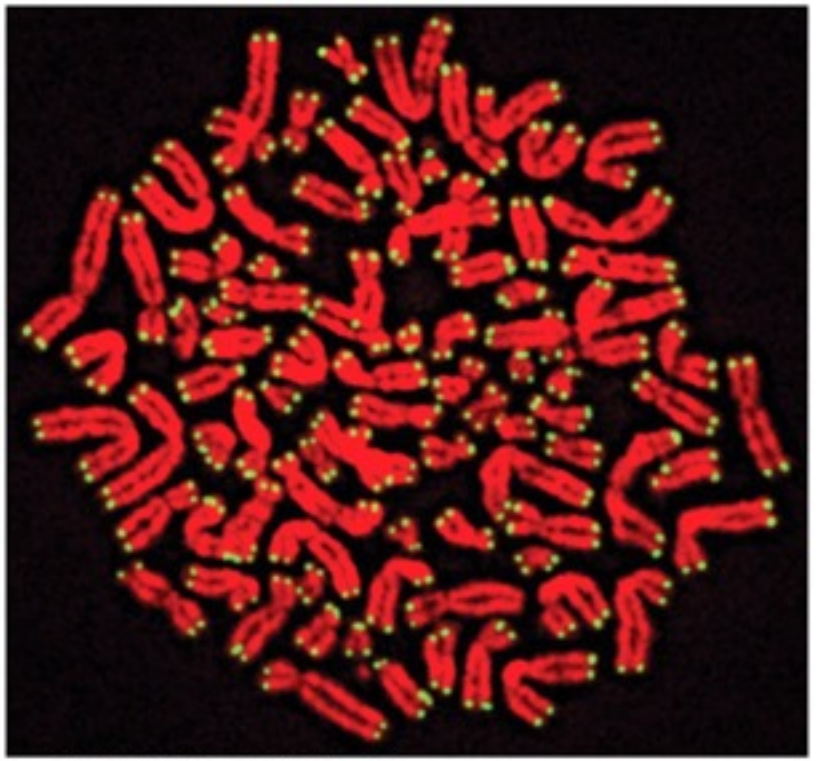
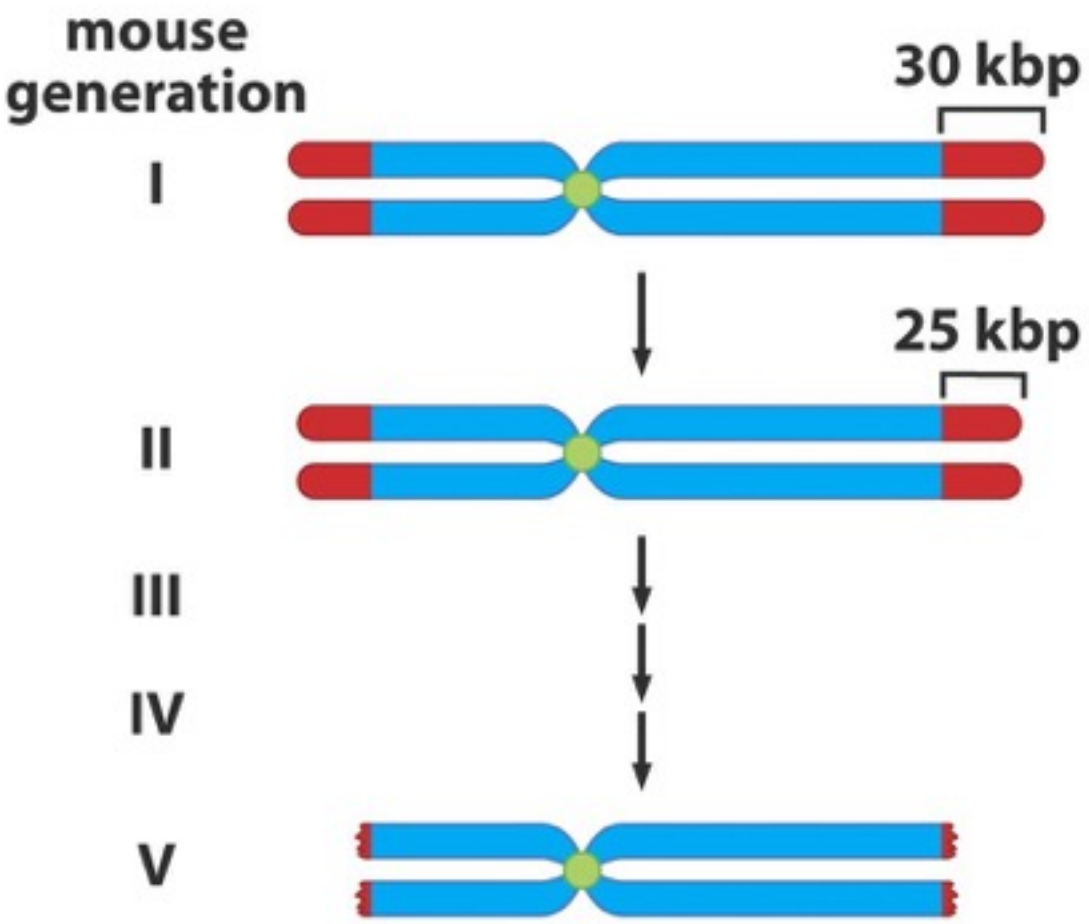


Figure 10-11a The Biology of Cancer (© Garland Science 2007)



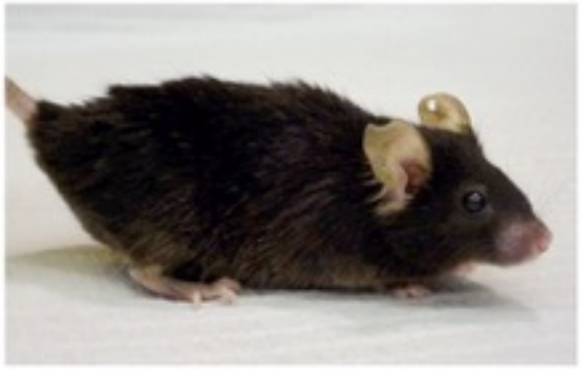


Figure 10-31 The Biology of Cancer (© Garland Science 2007)

Mice (mTR-/-) are healthy until second and third generation, by 4^{th} and 5^{th} present premature signs of aging, incapable of healing wounds, loss of muscle tissue and hunched back

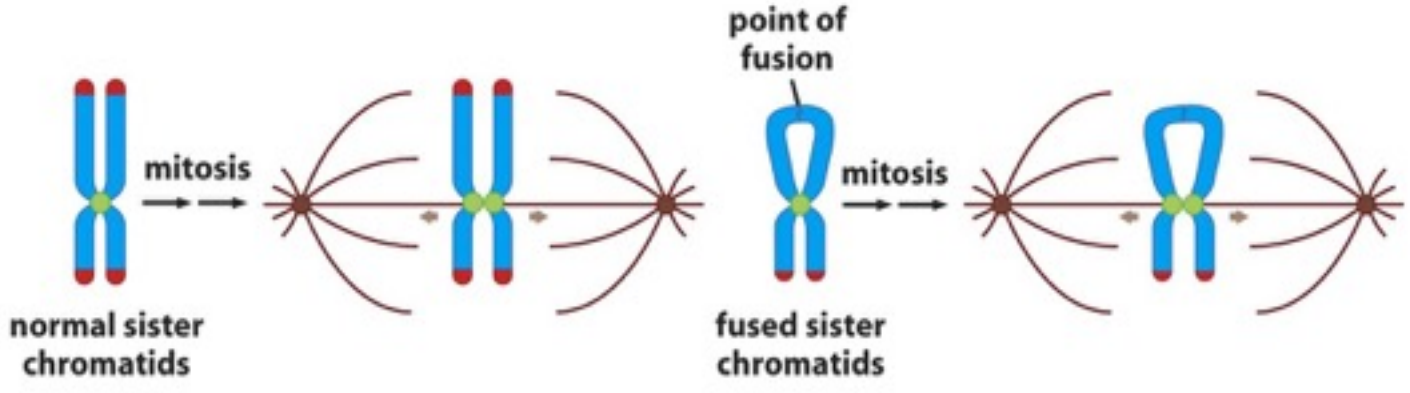


Figure 10-14b The Biology of Cancer (© Garland Science 2007)

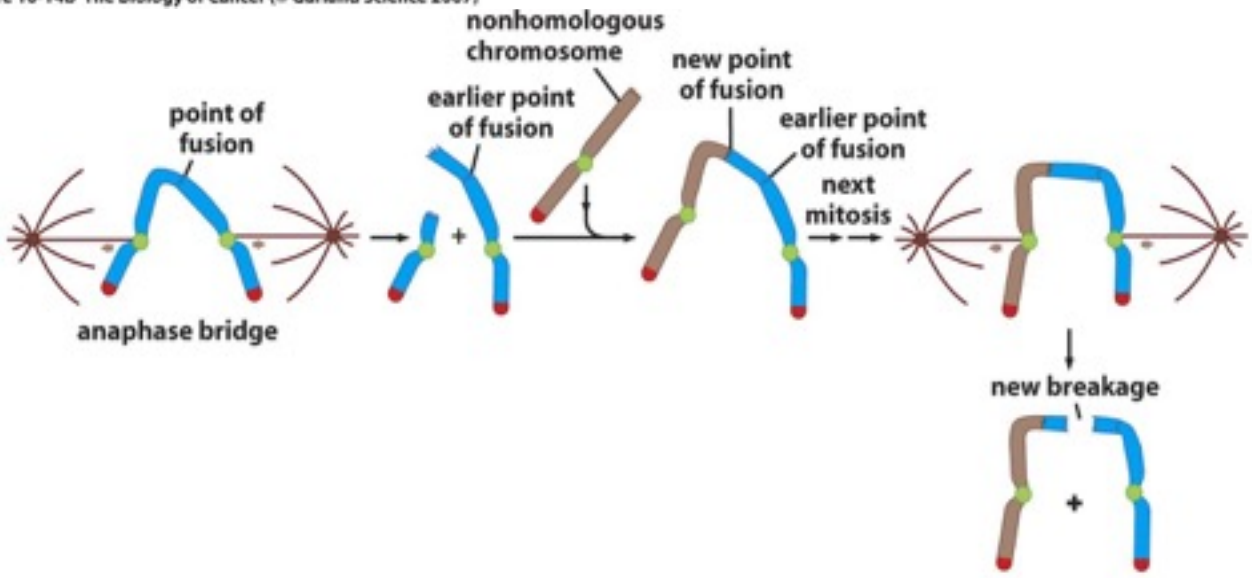
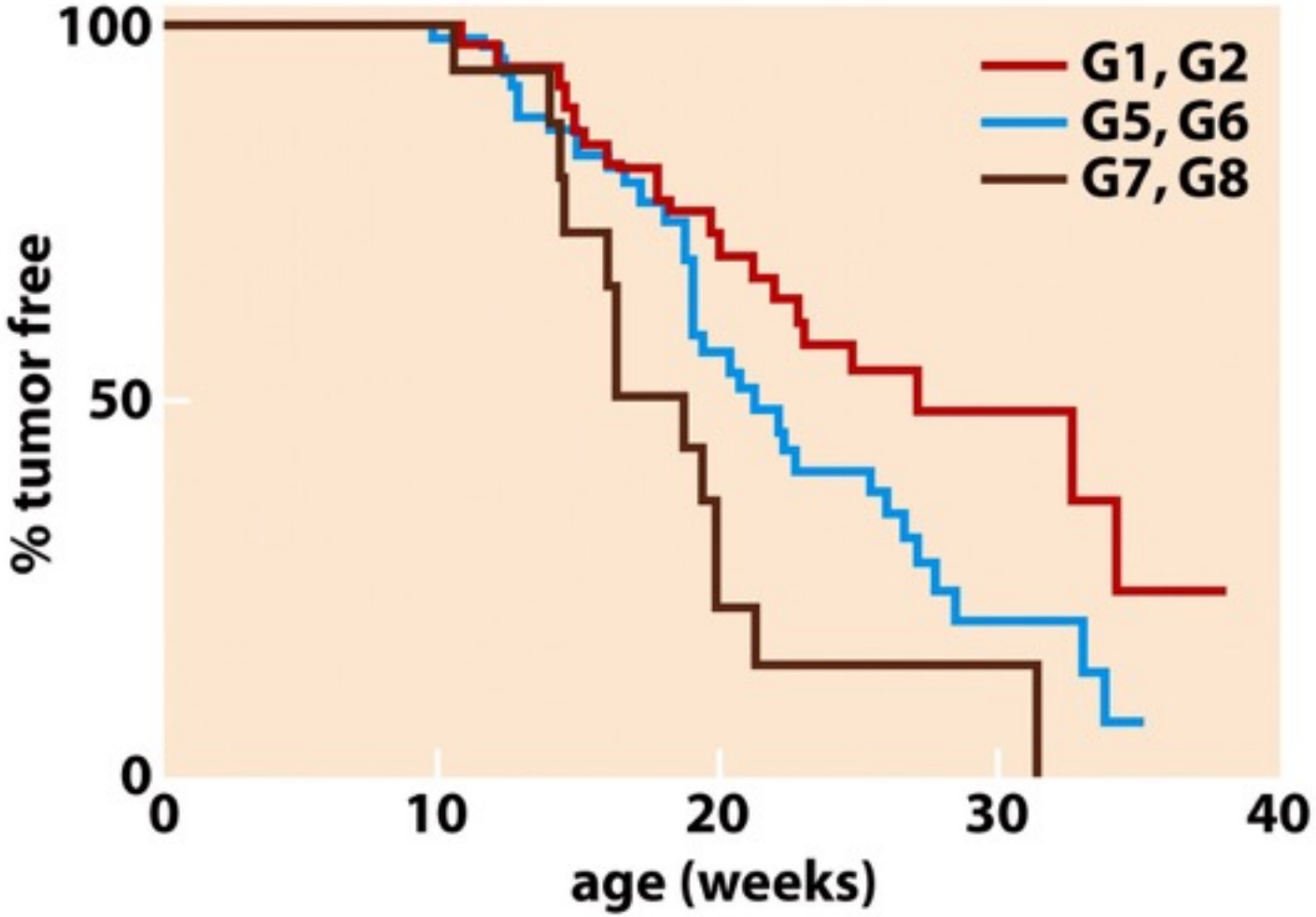


Figure 10-14c The Biology of Cancer (© Garland Science 2007)



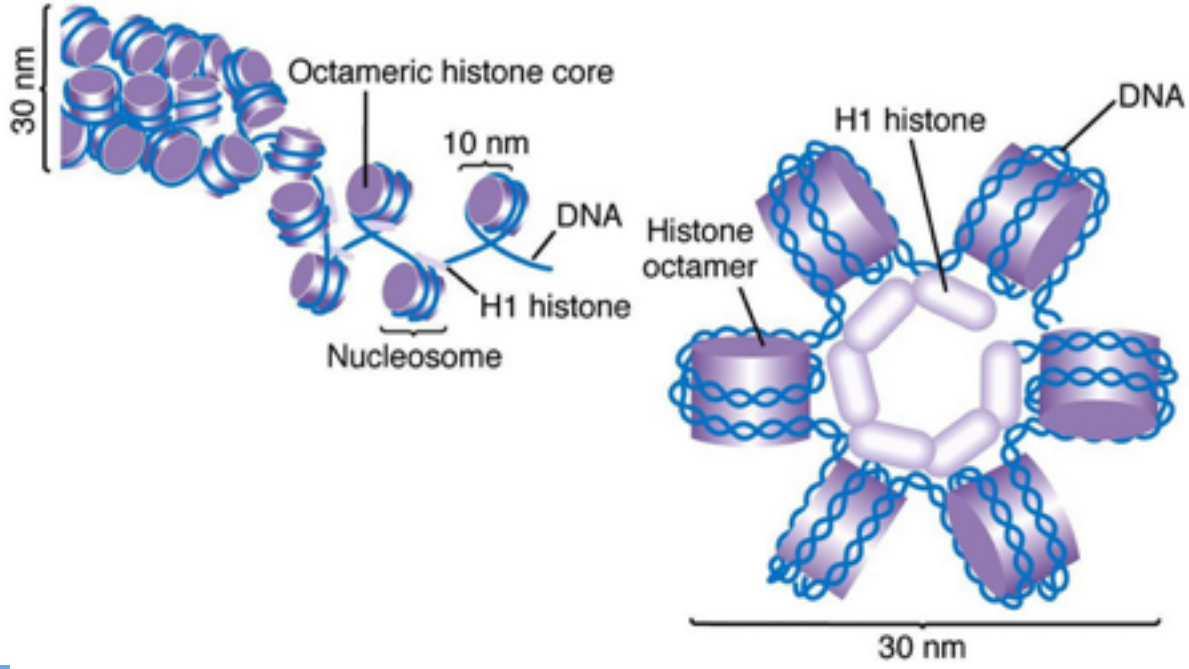
Tumor incidence in mTR-/- p53-/- mice
By the 7th generation already 50% of the mice show tumors by the age of 17 weeks

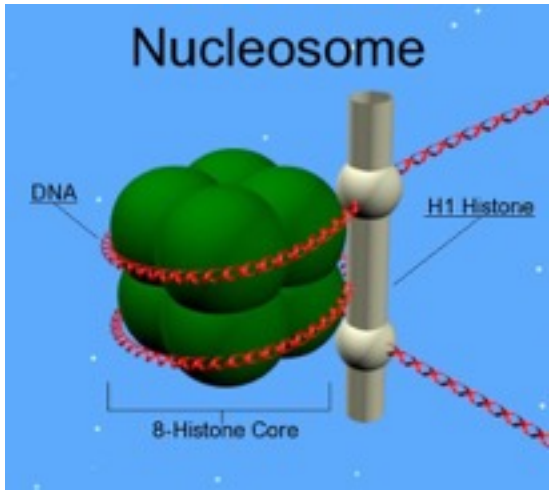
Figure 10.34 *The Biology of Cancer* (© Garland Science 2007)

HISTONE PROTEINS - NUCLEOSOME

HISTONES:

Positive charged proteins that wrap DNA up





NUCLEOSOME

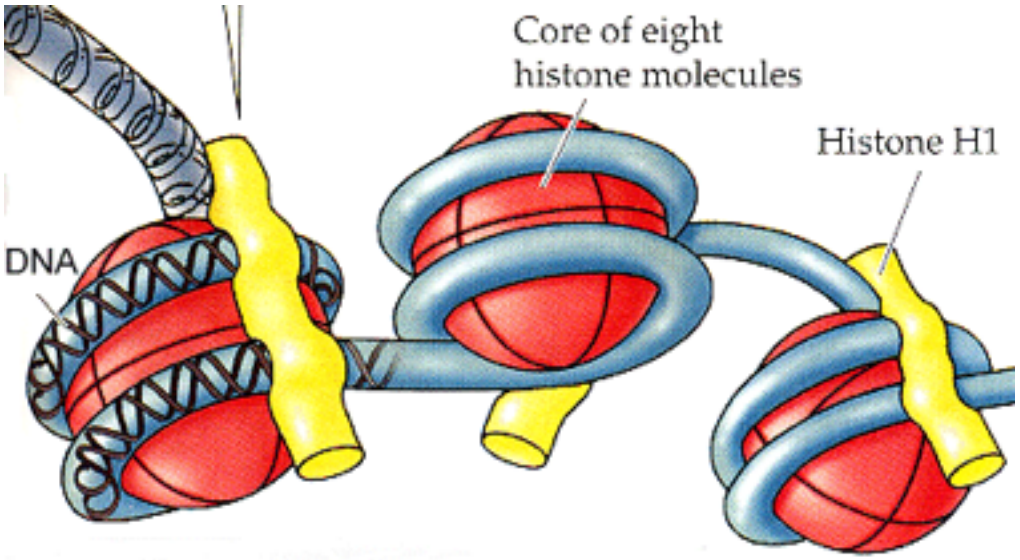
DNA-Histone complex formed by eight histone molecules

2x H3-H4

2x H2A-H2B

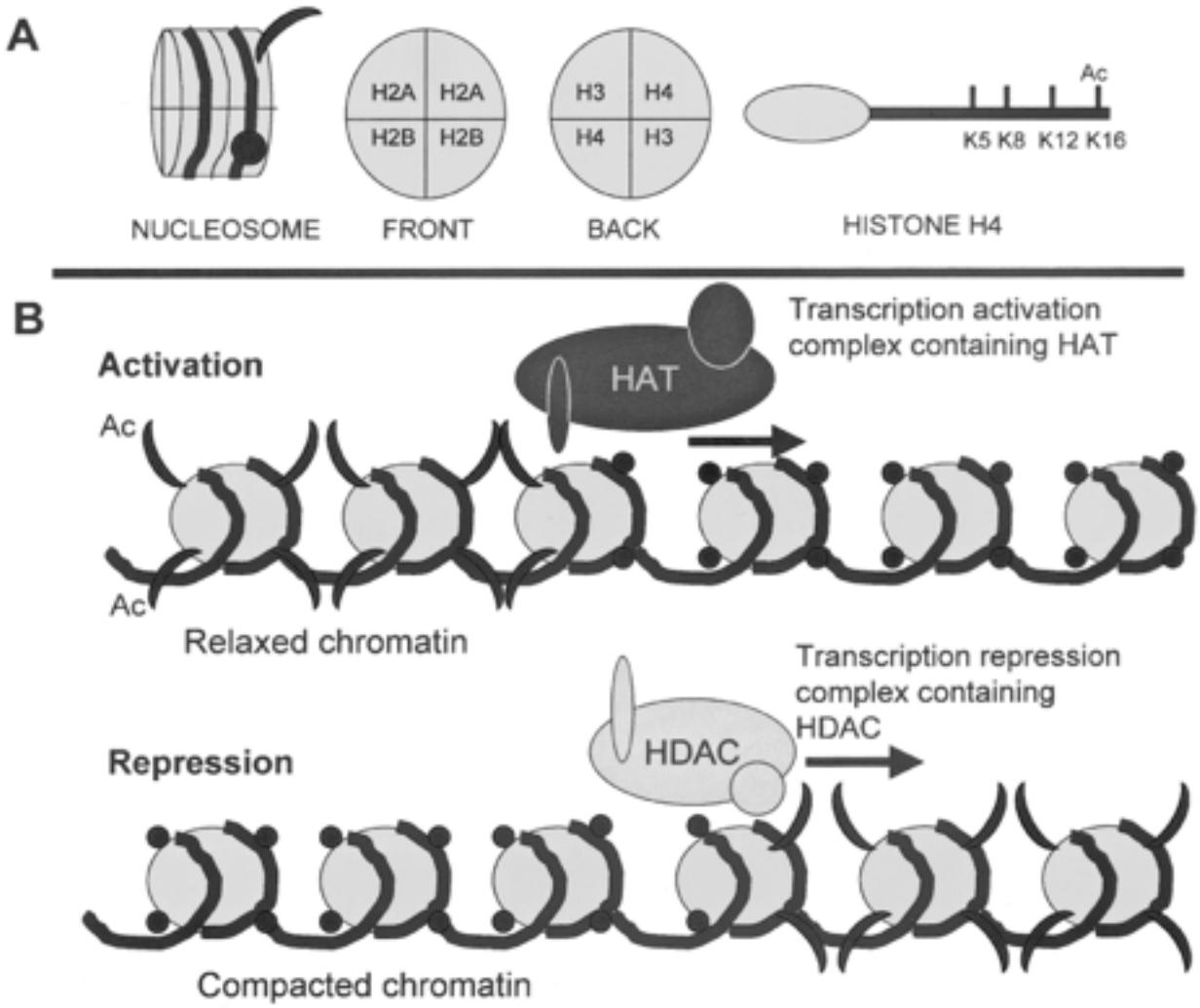
Kept together by H1 histone

Nucleosomes have two turns of DNA

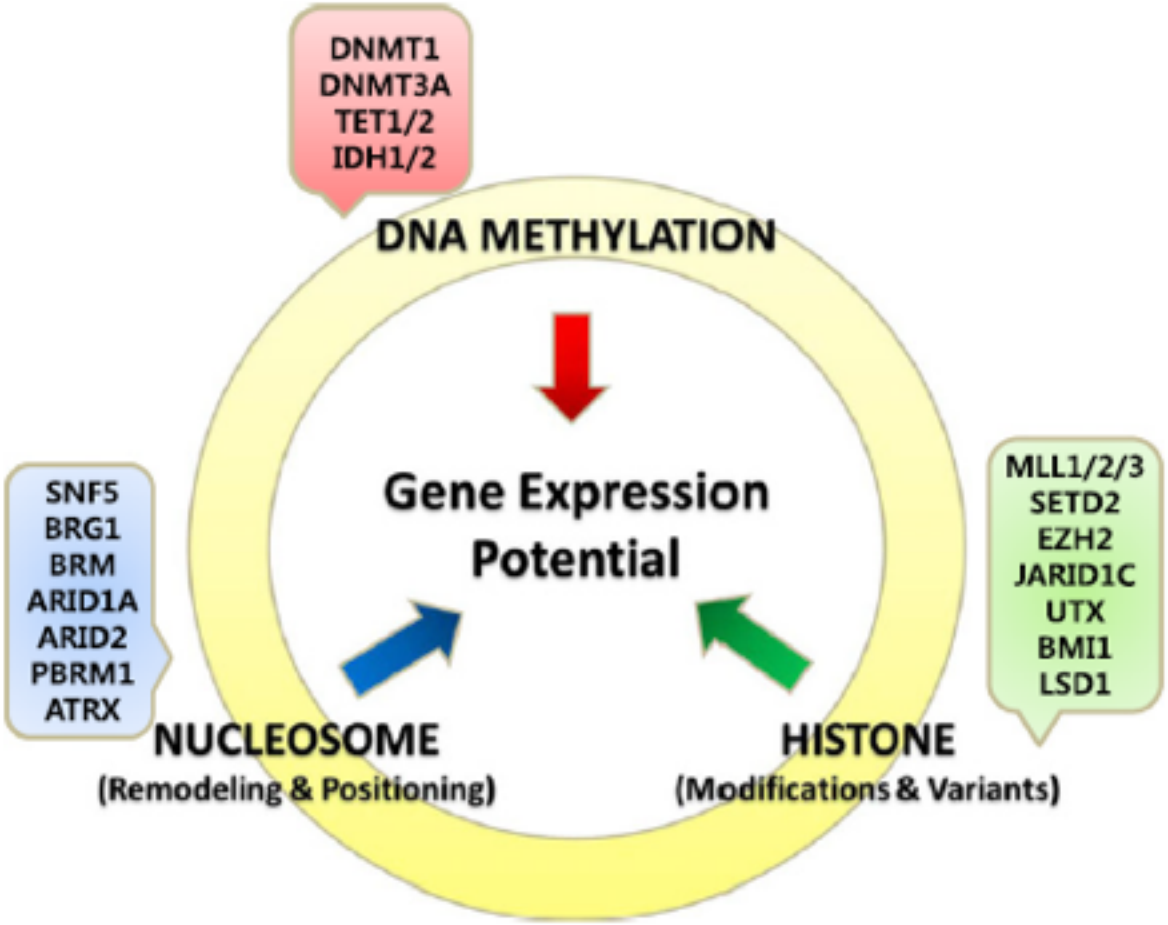


The length of DNA per nucleosome varies for individual tissues (~150bp)

HISTONE MODIFICATIONS

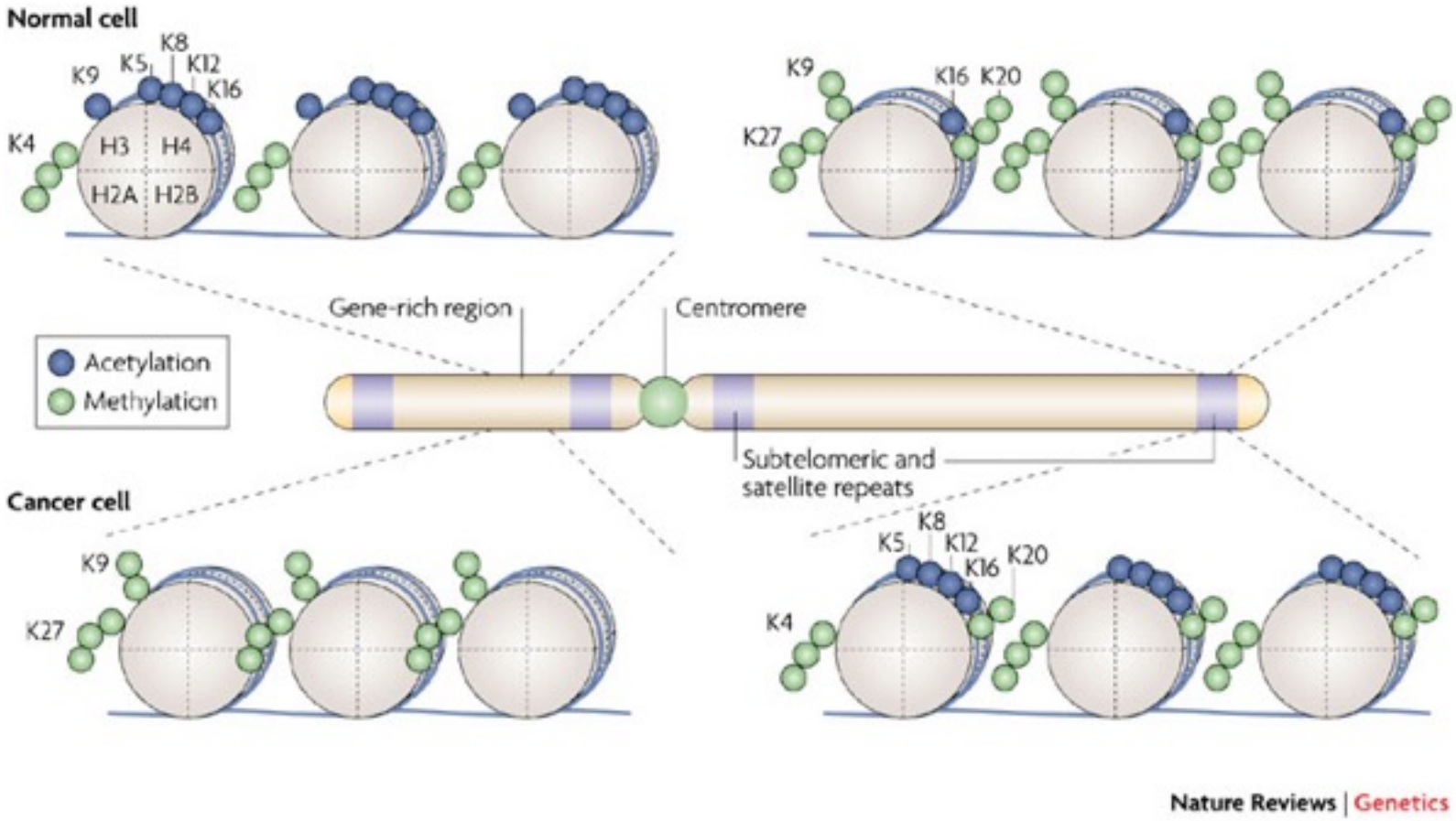


Biochemical Journal (2003) Volume **370**, 737-749



Cancer Genetics and Epigenetics: Two Sides of the Same Coin?
Jueng Soo You and Peter A. Jones – Cancer Cell, 22, July 10, 2012

HISTONE MODIFICATIONS



Nature Reviews Genetics **3**, 662-673 (September 2002)

PART 1
DNA REPLICATION

DNA REPLICATION – CELL DIVISION

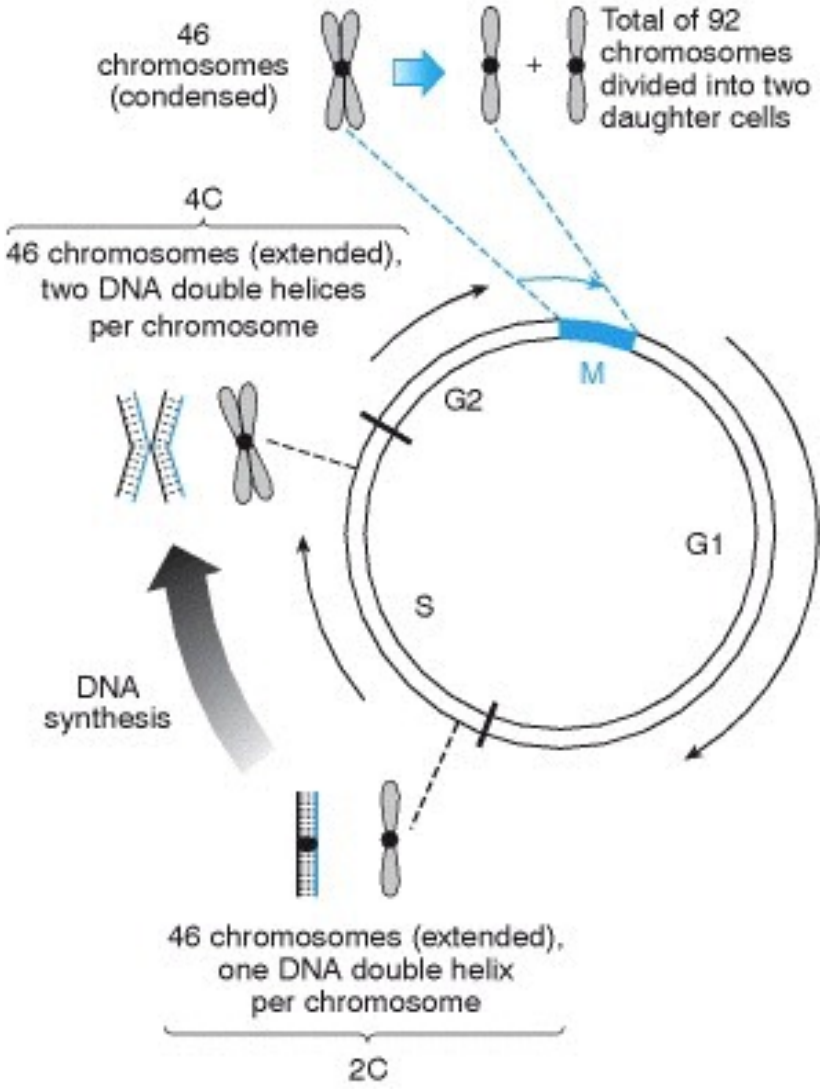
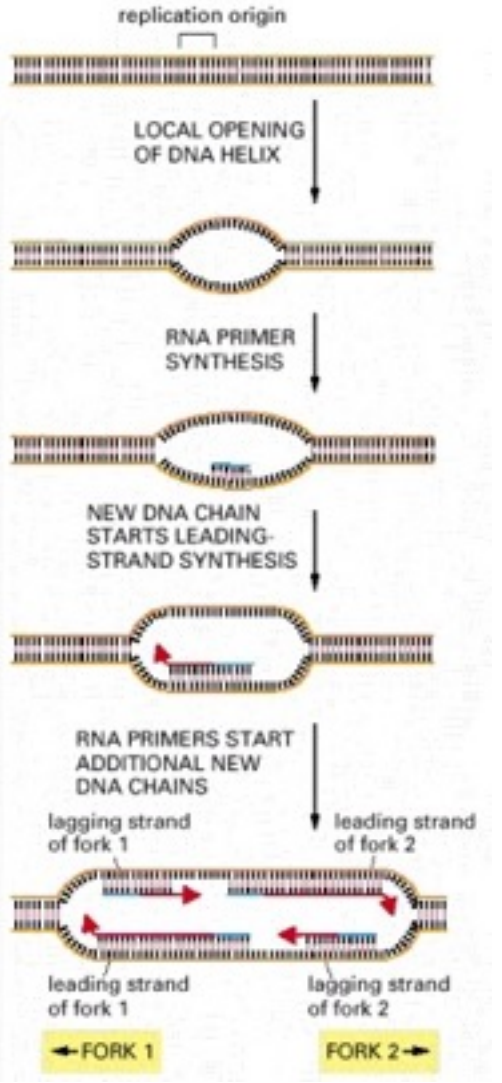


Image from
Human Molecular Genetics. 2nd edition.
Strachan T, Read AP.
New York: Wiley-Liss; 1999.

DNA REPLICATION – CELL DIVISION

- DNA has to be replicated ONLY ONCE per cell division

1. DNA opens (DNA elicase)
2. Synthesis of new complementary strand



- DNA synthesis happens only in one direction (5’ → 3’)…
- But complementary strands have opposite directions
- ….OKAZAKI FRAGMENTS….

- Extended from RNA primers
- ~100-200 bp
- Gaps filled by DNA polymerase
- DNA fragments sealed by DNA ligase

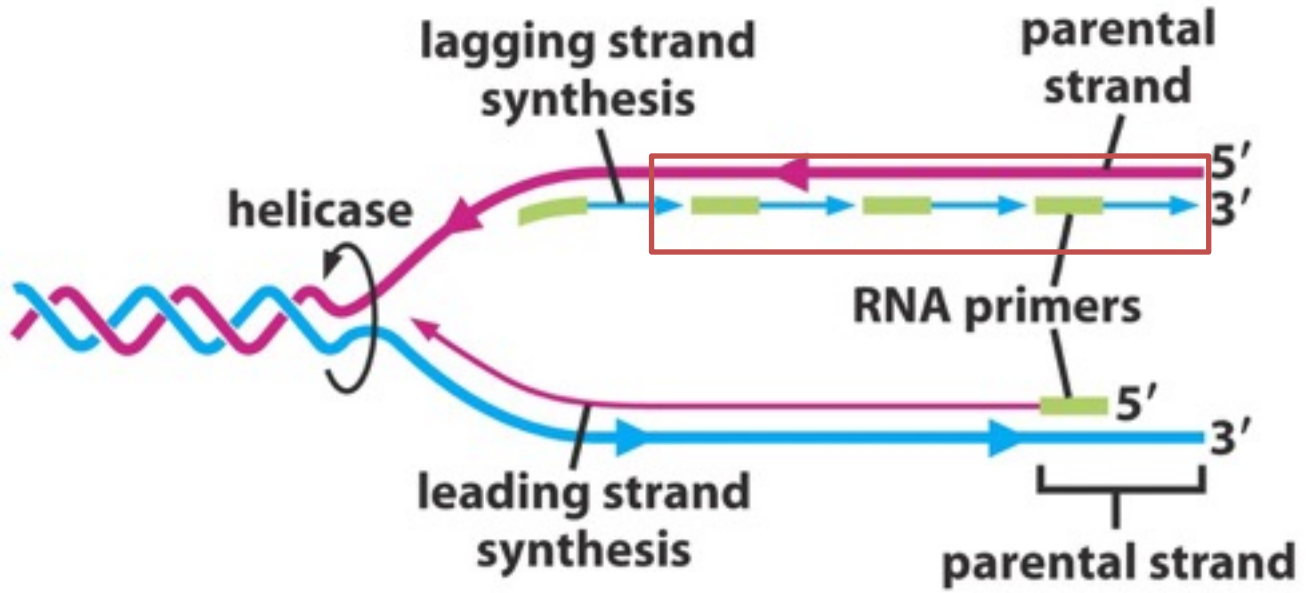
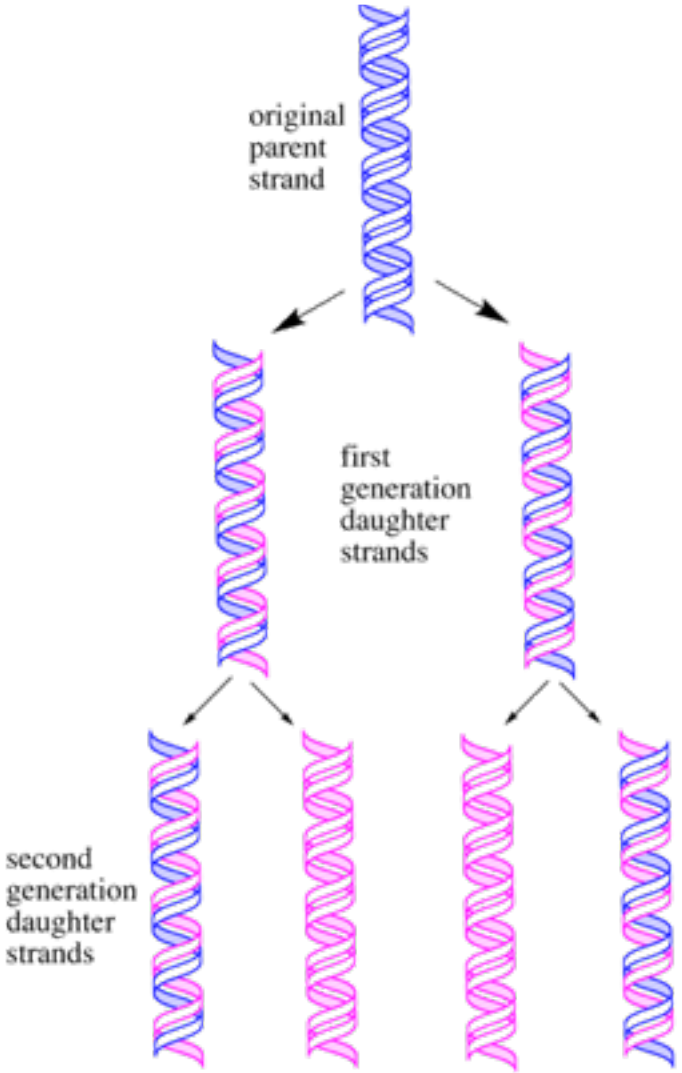


Figure 10.20 *The Biology of Cancer* (© Garland Science 2007)

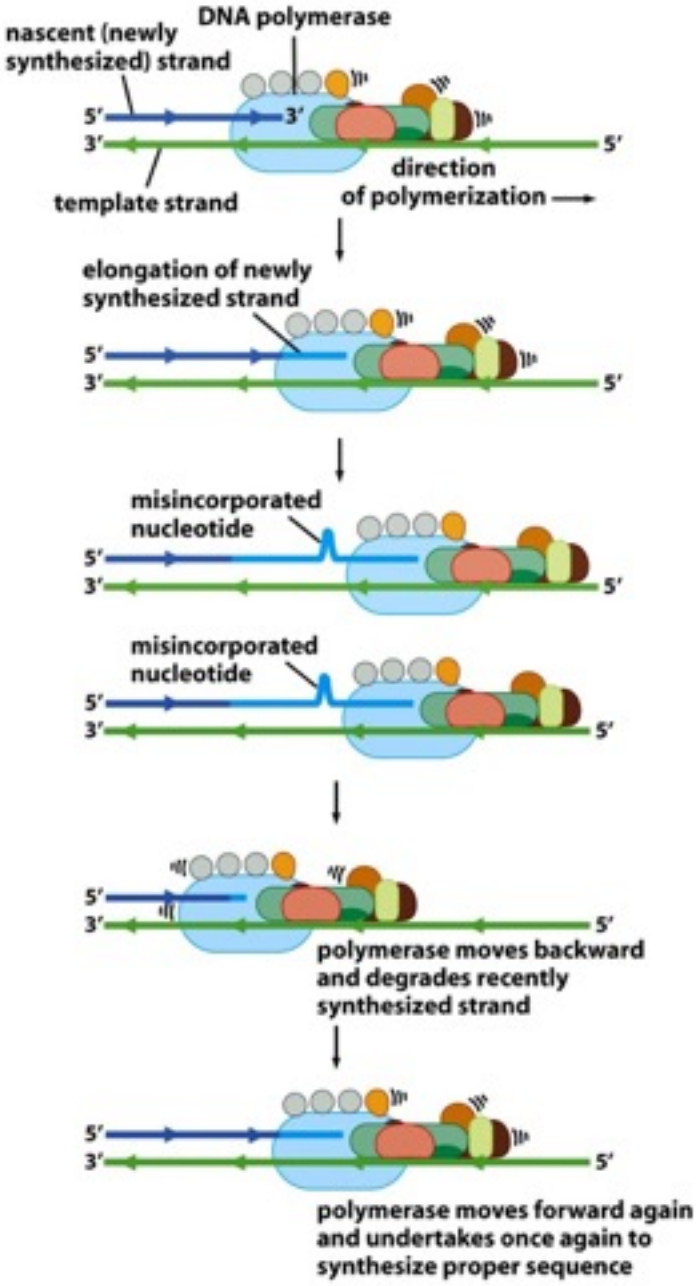
SEMICONSERVATIVE PROCESS



- REPLICON: region where DNA replication happens
  - Origin of replication
  - Terminus
- Several replicons in each chromosome

- Replication ends at the telomeric region, this **shortens** the length of the telomeres in the daughter cell
- => cells can replicate just a **limited number of times** (remember mTR-/-) mice?)

ERRORS DURING DNA REPLICATION



- DNA Pol complex is not perfect, rate of 1 every 10.000bp mismatches
- Proofread ~99% of its own mismatches → 1/10.000.000 rate errors

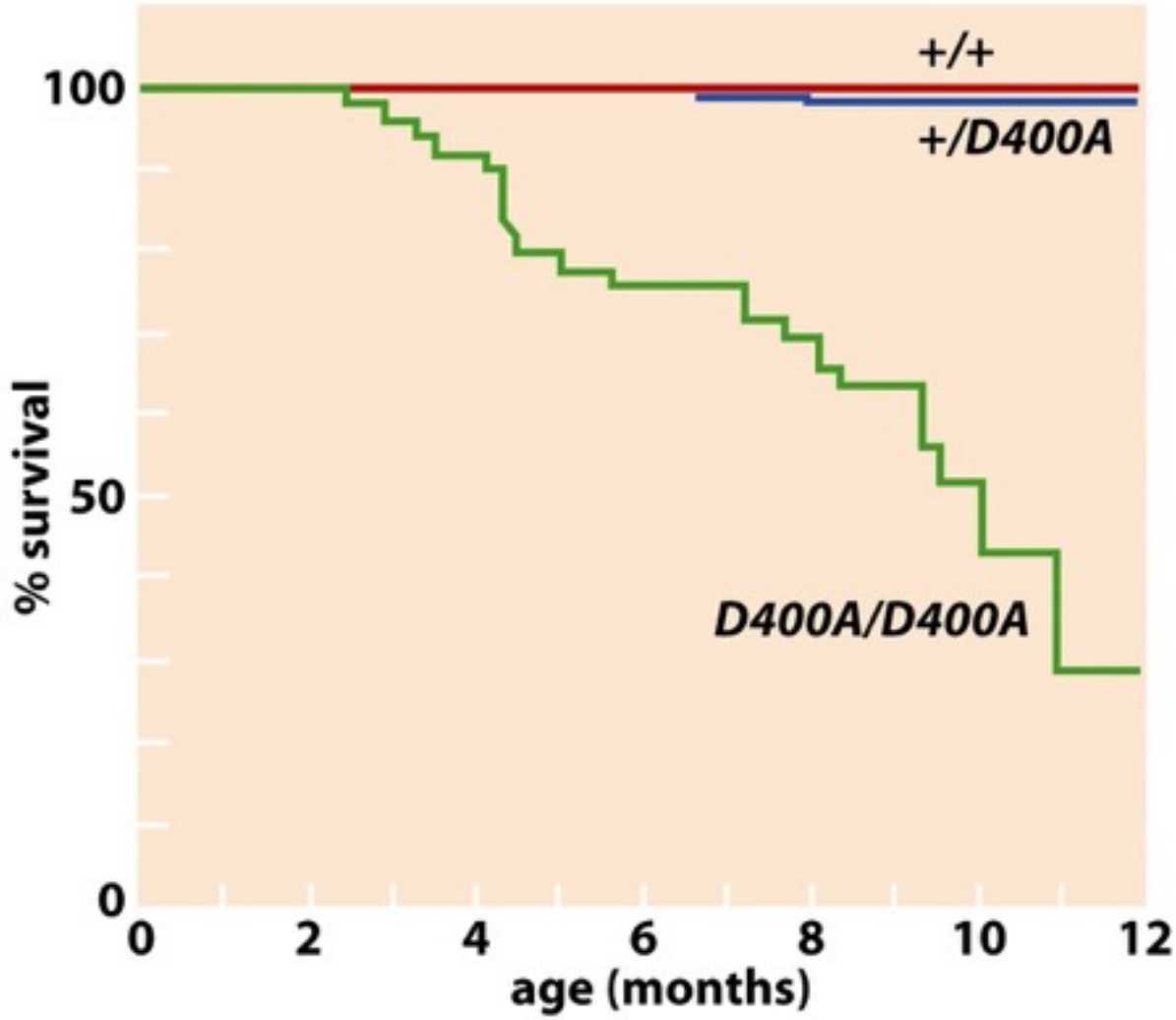
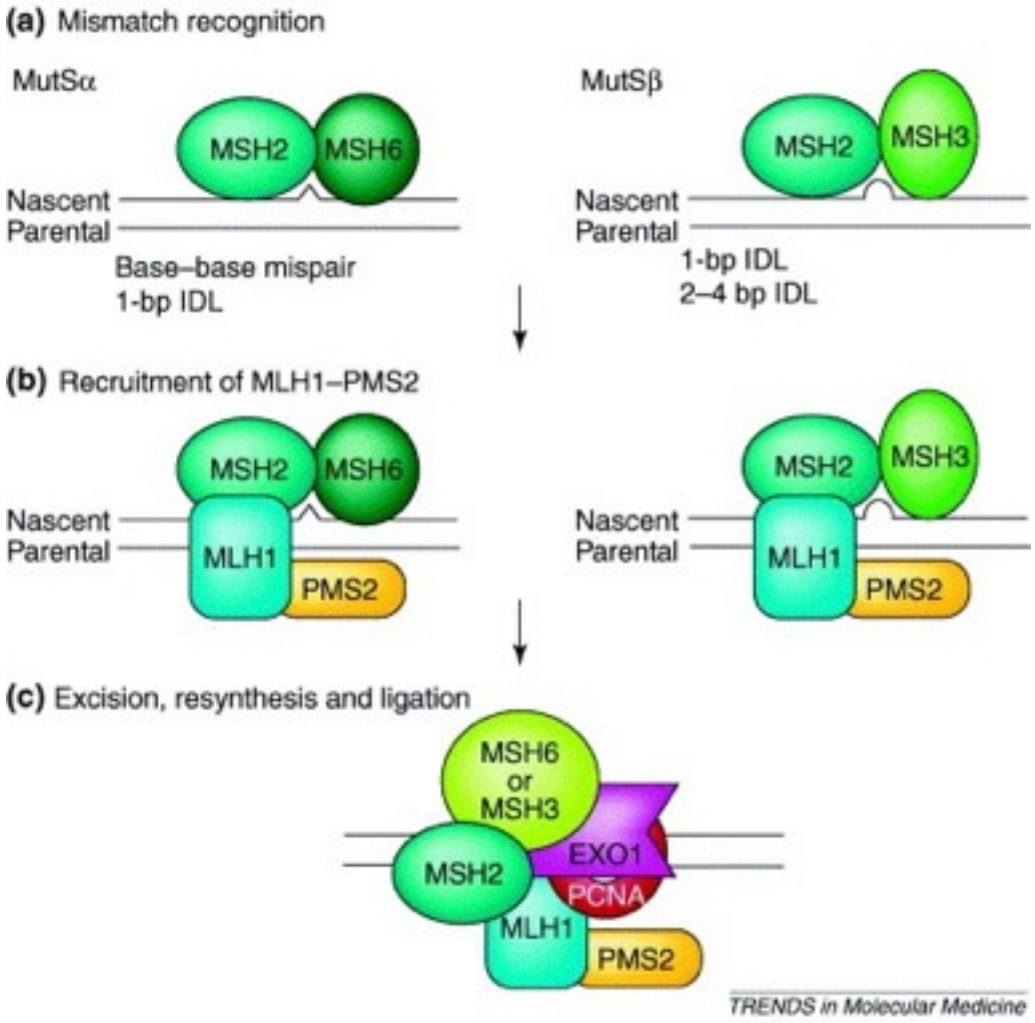


Figure 12-7 The Biology of Cancer (© Garland Science 2007)

+/+ = p53 WT
+/D400A = heterozygous
D400A/D400A= homozygous mutant

Point mutation in the pol-delta gene (D400A) is enough to block 3'->5" exonuclease activity and proofreading activity.

MISMATCH REPAIR (MMR)



- Set of enzymes that monitor the newly synthetized DNA to detect miscopied DNA sequences.

Mouse models for human DNA mismatch-repair gene defects
Kaichun Weia, Raju Kucherlapatib, Winfried Edelmanna,
Trends in Molecular Medicine
Volume 8, Issue 7, 1 July 2002, Pages 346-353

XERODERMA PIGMENTOSUM (XP)

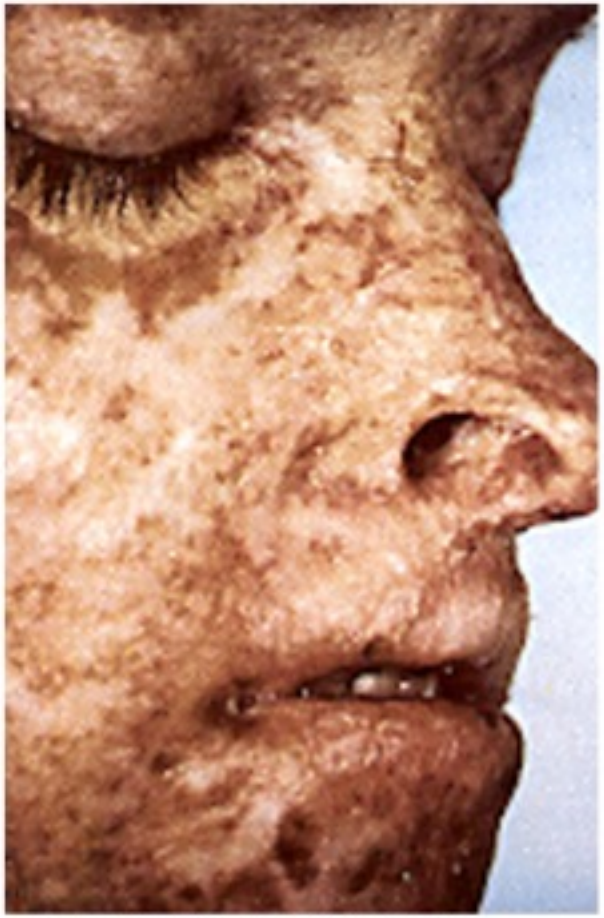


Figure 12-25 The Biology of Cancer (© Garland Science 2007)

Defects in ANY of the eight distinct genes involved in DNA repair lead to Xeroderma Pigmentosum

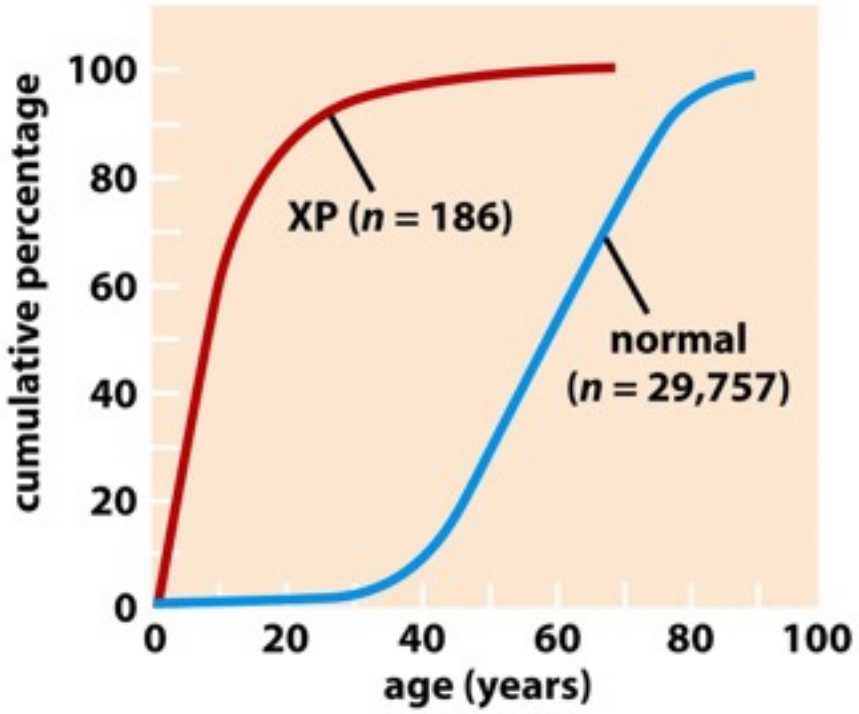


Figure 12-26 The Biology of Cancer (© Garland Science 2007)

- 1000-fold higher risk of skin cancer
- 100.000-fold higher risk of squamous cell carcinoma

Table 12.1 Human familial cancer syndromes due to inherited defects in DNA repair

Name of syndrome	Name of gene	Cancer phenotype	Enzyme or process affected
HNPCC	(4–5 genes)[a]	colonic polyposis	mismatch repair enzymes
XP[b]	(8 genes)[b]	UV-induced skin cancers	nucleotide-excision repair
AT[c]	*ATM*	leukemia, lymphoma	response to dsDNA breaks
AT-like disorder[c]	*MRE11*	not yet determined	dsDNA repair by NHEJ
Familial breast, ovarian cancer	*BRCA1, BRCA2*[d]	breast and ovarian carcinomas	homology-directed repair of dsDNA breaks
Werner	*WRN*	several cancers	exonuclease and DNA helicase[e], replication
Bloom	*BLM*	solid tumors	DNA helicase, replication
Fanconi anemia	(9 genes)[f]	AML, HNSCC	repair of DNA cross-links and ds breaks
Nijmegen break[g]	*NBS*	mostly lymphomas	processing of dsDNA breaks, NHEJ
Li–Fraumeni	*TP53*	multiple cancers	DNA damage alarm protein
Li–Fraumeni	*CHK2*	colon, breast	kinase signaling DNA damage

[a]Five distinct MMR genes are transmitted as mutant alleles in the human germ line. Two MMR genes—*MSH2* and *MLH1*—are commonly involved in HNPCC; two other MMR genes—*MSH6* and *PMS2*—are involved in a small number of cases; a fifth gene, *PMS1*, may also be involved in a small number of cases.

[b]Xeroderma pigmentosum, at least eight distinct genes, seven of which are involved in NER. The seven genes are named *XPA* through *XPG*. An eighth gene, *XPV*, encodes DNA polymerase η.

[c]Ataxia telangiectasia, small number of cases.

[d]Mutant germ-line alleles of *BRCA1* and *BRCA2* together may account for 10–20% of identifiable human familial breast cancers.

[e]An exonuclease digests DNA or RNA from one end inward; a DNA helicase unwinds double-stranded DNA molecules.

[f]Nine genes have been cloned and at least eleven complementation groups have been demonstrated. Complementation group J encodes the BACH1 protein, the partner of BRCA1.

[g]The NBS1 protein (termed nibrin) forms a physical complex with the Rad50 and Mre11 proteins, all of which are involved in repair of dsDNA breaks. The phenotypes of patients with Nijmegen break syndrome are similar but not identical to those suffering from AT.

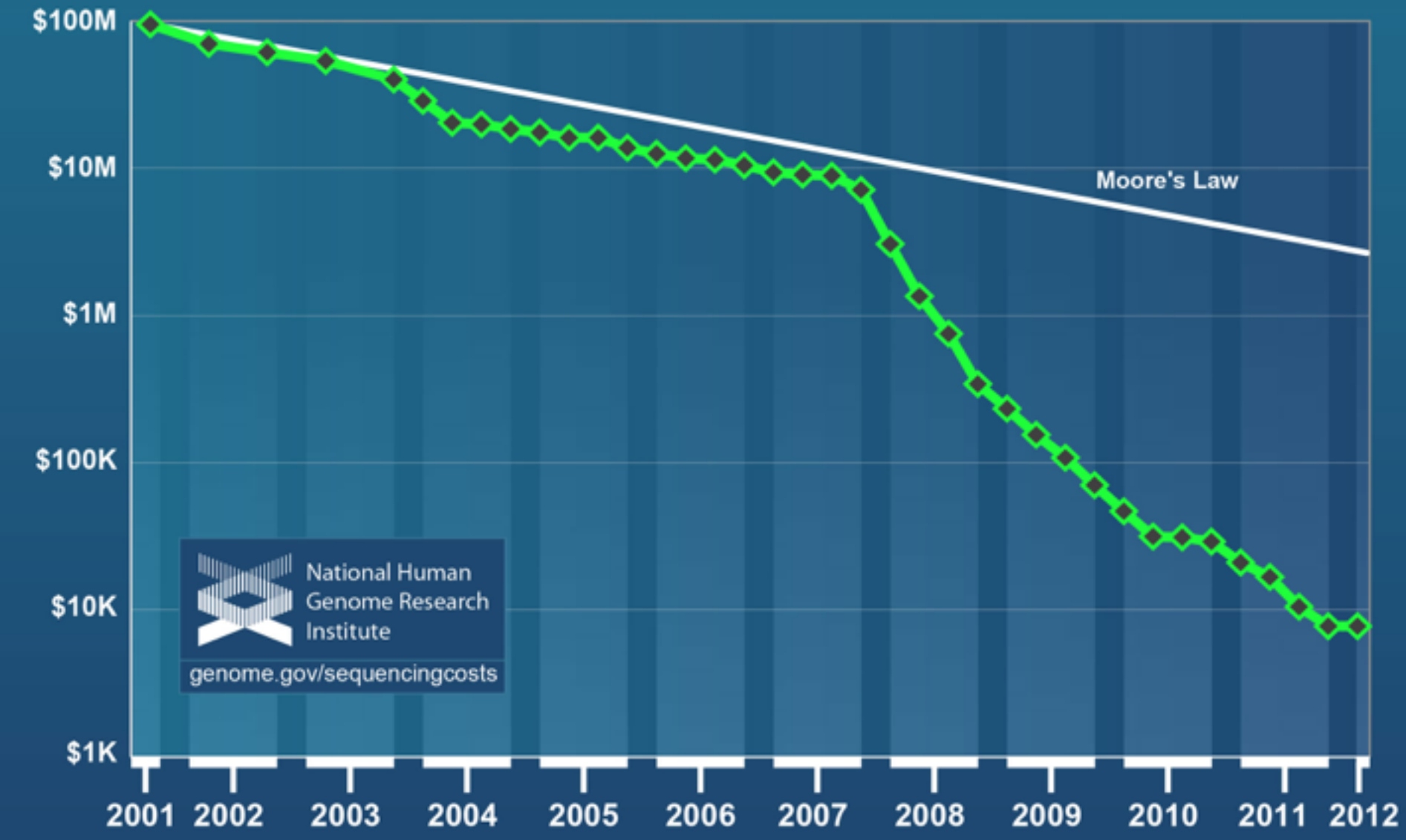
Adapted in part from B. Alberts et al., Molecular Biology of the Cell, 4th ed. New York: Garland Science, 2002; and from E.R. Fearon, *Science* 278:1043–1050, 1997.

Table 12.1 *The Biology of Cancer* (© Garland Science 2007)

GENOME SEQUENCING

- Charles DeLisi at the US Dept of Energy began to develop plans to map and sequence the human genome (money and politics were a big problem)
- Later (1991) Craig Venter invented Expressed Seq Tag (EST) to quickly identify genes.
- In 1998 helped creating Celera Genomics and in 2000 they finished the Drosophila genome with shotgun seq

Cost per Genome



CANCER GENOME PROJECT

Perspectives

Nature **464**, 993-998 (15 April 2010) | doi:10.1038/nature08987

There is a Corrigendum (17 June 2010) associated with this document.

International network of cancer genome projects

The International Cancer Genome Consortium

The International Cancer Genome Consortium (ICGC) was launched to coordinate large-scale cancer genome studies in tumours from 50 different cancer types and/or subtypes that are of clinical and societal importance across the globe. Systematic studies of more than 25,000 cancer genomes at the genomic, epigenomic and transcriptomic levels will reveal the repertoire of oncogenic mutations, uncover traces of the mutagenic influences, define clinically relevant subtypes for prognosis and therapeutic management, and enable the development of new cancer therapies.

▲ Top

Table 1. Current Large-Scale Cancer Genome Projects[a]

Anatomic Site	Tumor Type
Brain/Central nervous system	glioblastoma multiforme
	low-grade glioma
	pediatric: medulloblastoma
	pediatric: pilocytic astrocytoma
Head and neck	head/neck squamous cell cancer
	thyroid carcinoma
Thoracic	lung adenocarcinoma
	lung squamous cell carcinoma
Breast	breast lobular carcinoma
	breast ductal carcinoma
	breast triple-negative
	breast HER-2 positive
	breast ER positive vs. negative
Gastrointestinal	esophageal adenocarcinoma
	esophageal squamous carcinoma
	gastric adenocarcinoma
	gastric (intestinal/diffuse)
	hepatocellular (alcohol/adiposity)
	hepatocellular (virus)
	hepatocellular (general)
	pancreatic adenocarcinoma
	colorectal adenocarcinoma
	colon cancer (non-Western)
Gynecologic	ovarian serous cystadenocarcinoma
	endometrial carcinoma
	cervical cancer (squamous + adeno)
Urologic	renal: clear cell carcinoma
	renal: papillary carcinoma
	renal: chromophobe carcinoma
	bladder cancer
	prostate adenocarcinoma
	prostate adenocarcinoma, early onset
Skin	melanoma, cutaneous
Soft tissue (Sarcoma)	solitary fibrous tumors
	desmoid tumors
	angiorsarcomas
	leiomyosarcomas
	extraskeletal myxoid chondrosarcomas
Hematologic	acute myeloid leukemia
	lymphoma: chronic lymphocytic leuk.
	lymphoma: germinal B cell
	lymphoma: diffuse large B cell
	chronic myeloid disorders

[a]In conjunction with The Cancer Genome Atlas, International Cancer Genome Consortium, and Slim Initiative for Genomic Medicine.

Figure 9.1 Laboratory workflow for whole-genome sequencing.

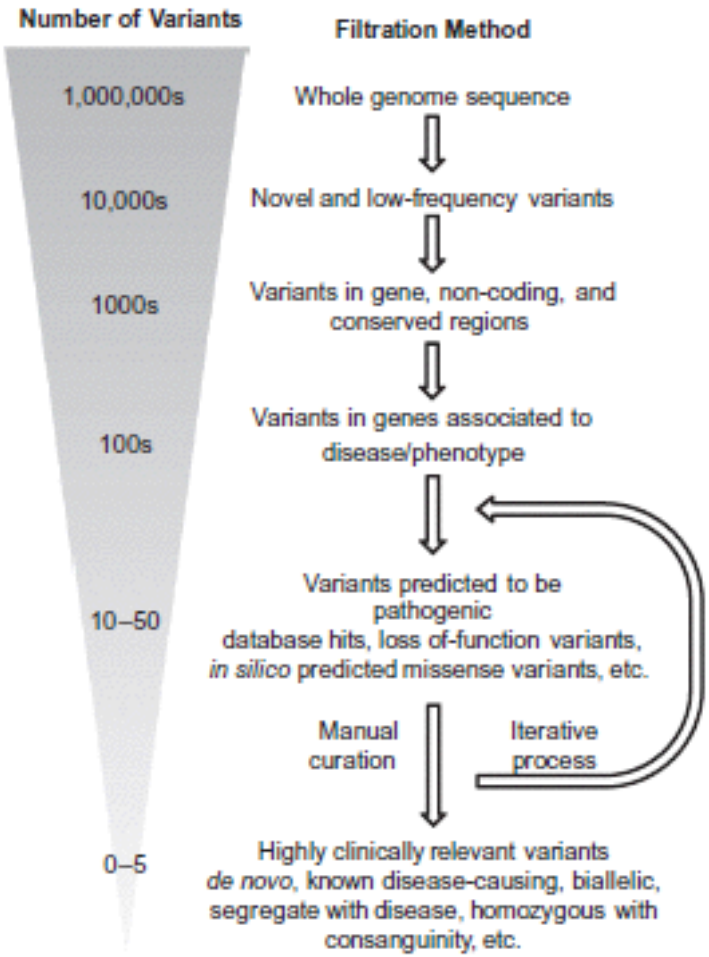


Figure 9.2 Variant analysis and filtration in whole-genome sequencing.

Clinical Genome Sequencing – Robert Green, Heidi Rehm and Isaac Kohane
Genomic and Personalized Medicine, 2nd ed. 2013

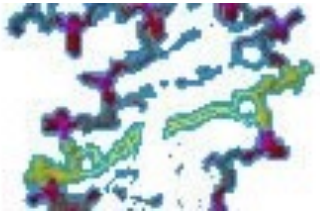
Mutations

- Frequency varies:
  - one base substitution per exome (i.e. some pediatric cancers)
  - Thousands of mutations per exomes (i.e. lung cancer, melanoma)
- SNPs: Single Nucleotide Polymorphism
  - Variation that occurrs in ~1% of the population

SNPs - GWAS

- Genome Wide association Studies
  - Find statistically significant association between genetic “marks” and a disease
  - Correlation does NOT mean causality!
  - Linkage disequilibrium (do two/more traits associate more than you would normally expect?)

dbSNP
Short Genetic Variations



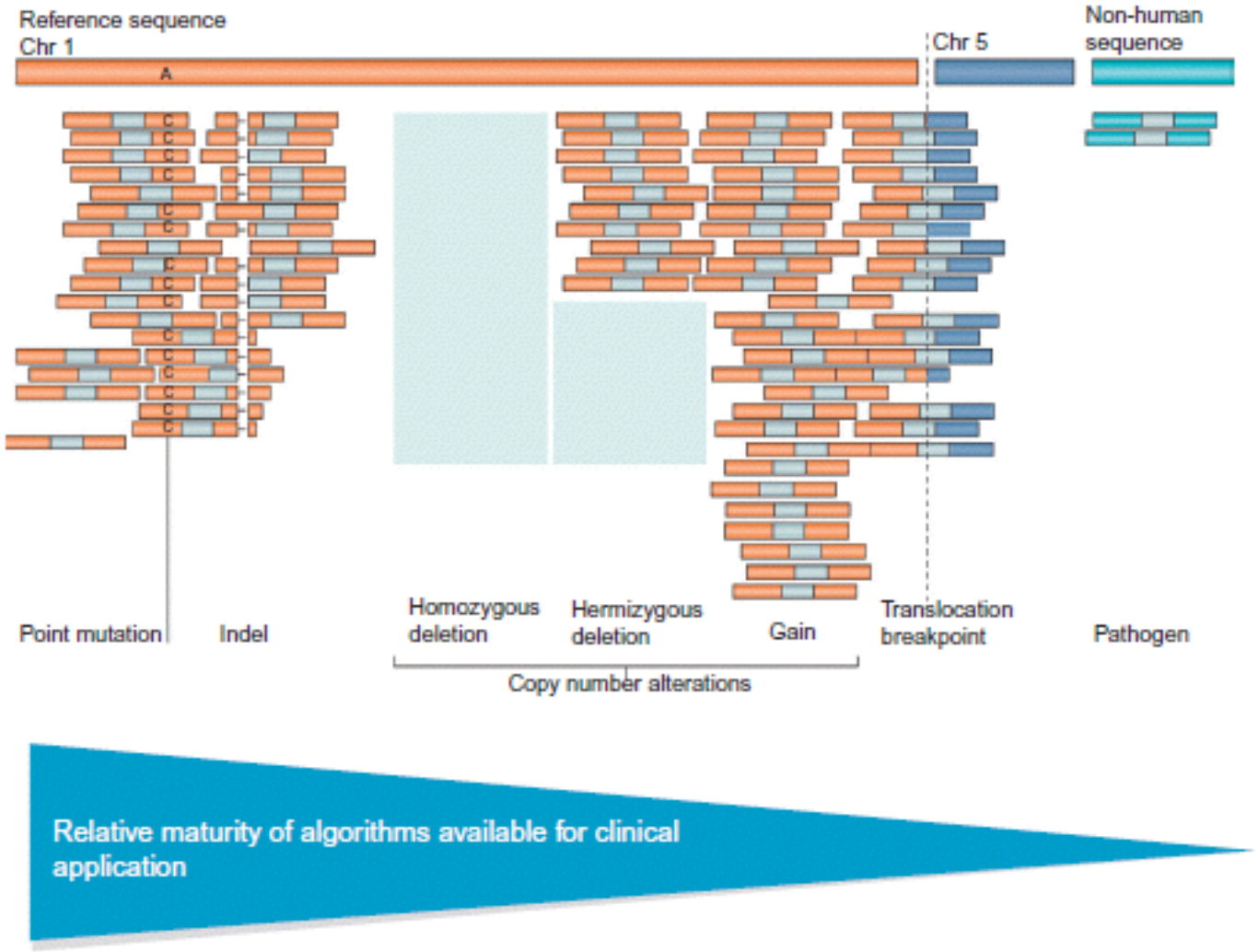
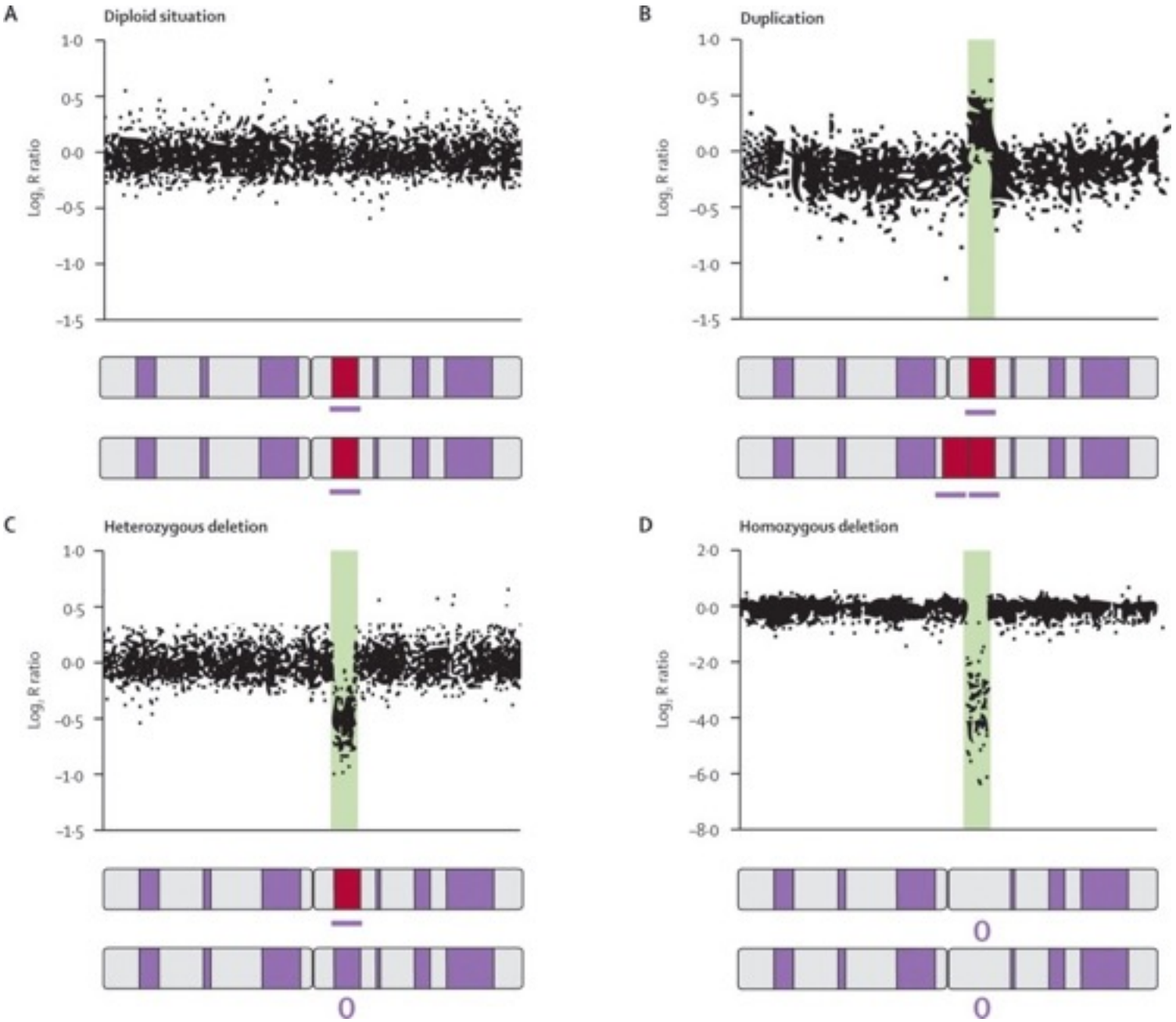


Figure 9.4 Types of genome alteration that can be detected by second-generation sequencing. *Reproduced from Meyerson et al., 2010.*

Clinical Genome Sequencing – Robert Green, Heidi Rehm and Isaac Kohane
Genomic and Personalized Medicine, 2nd ed. 2013



Copy-number variation in sporadic amyotrophic lateral sclerosis: a genome-wide screen
Hylke M Blauw et al – The Lancet, Neurology – April 2008

BRCA example

845G → A mutation in HFE gene
Hemochromatosis

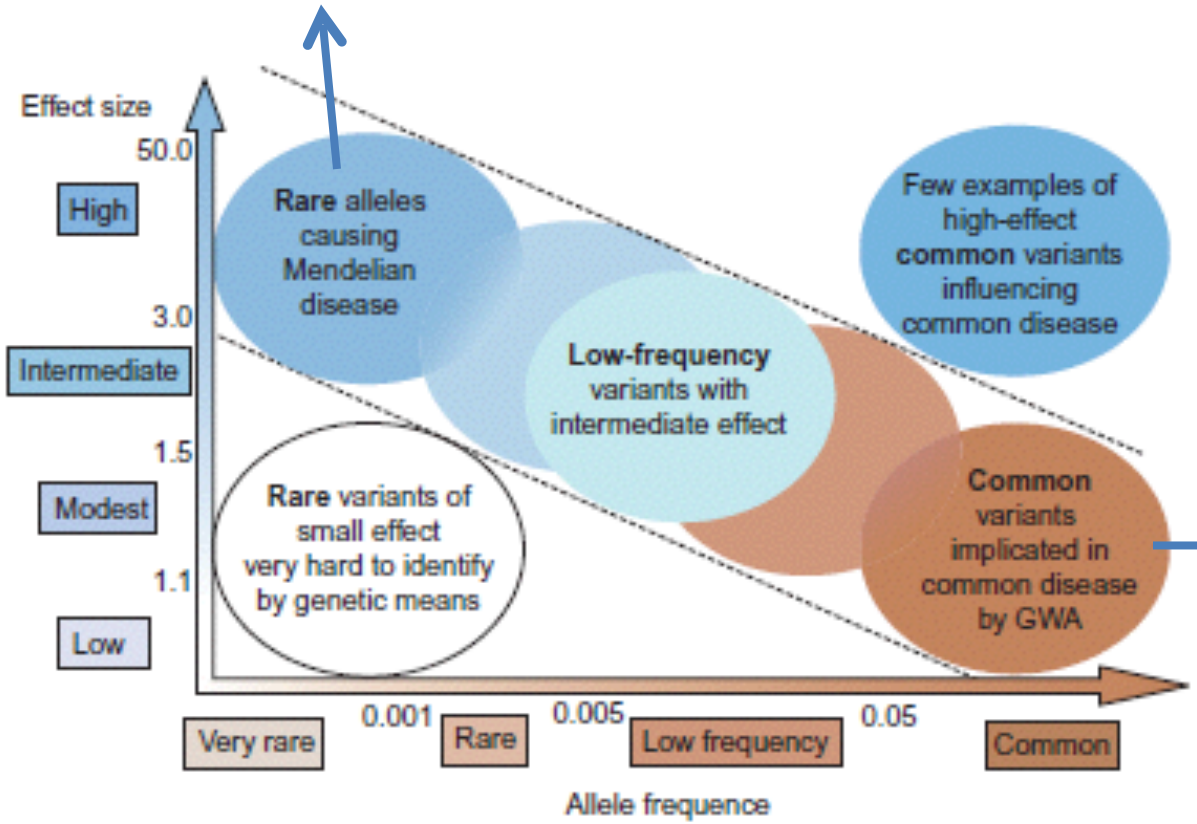


Figure 9.5 The spectrum of risk associated with rare and common genetic variants. *Figure reproduced from Manolio et al., 2009, cited in that paper as modified from a similar figure in McCarthy et al., 2008.*

SO….

- DNA packed up really tightly into chromosomes
- Several regions open up at the same moment to start DNA replication
- DNA replication is not perfect and introduces mutations
- Lack of efficient DNA repair mechanisms can lead to cancer
- Current sequencing technology helped profiling DNA variations that associate with/lead to diseases

PART 2
TRANSCRIPTION

TRANSCRIPTION

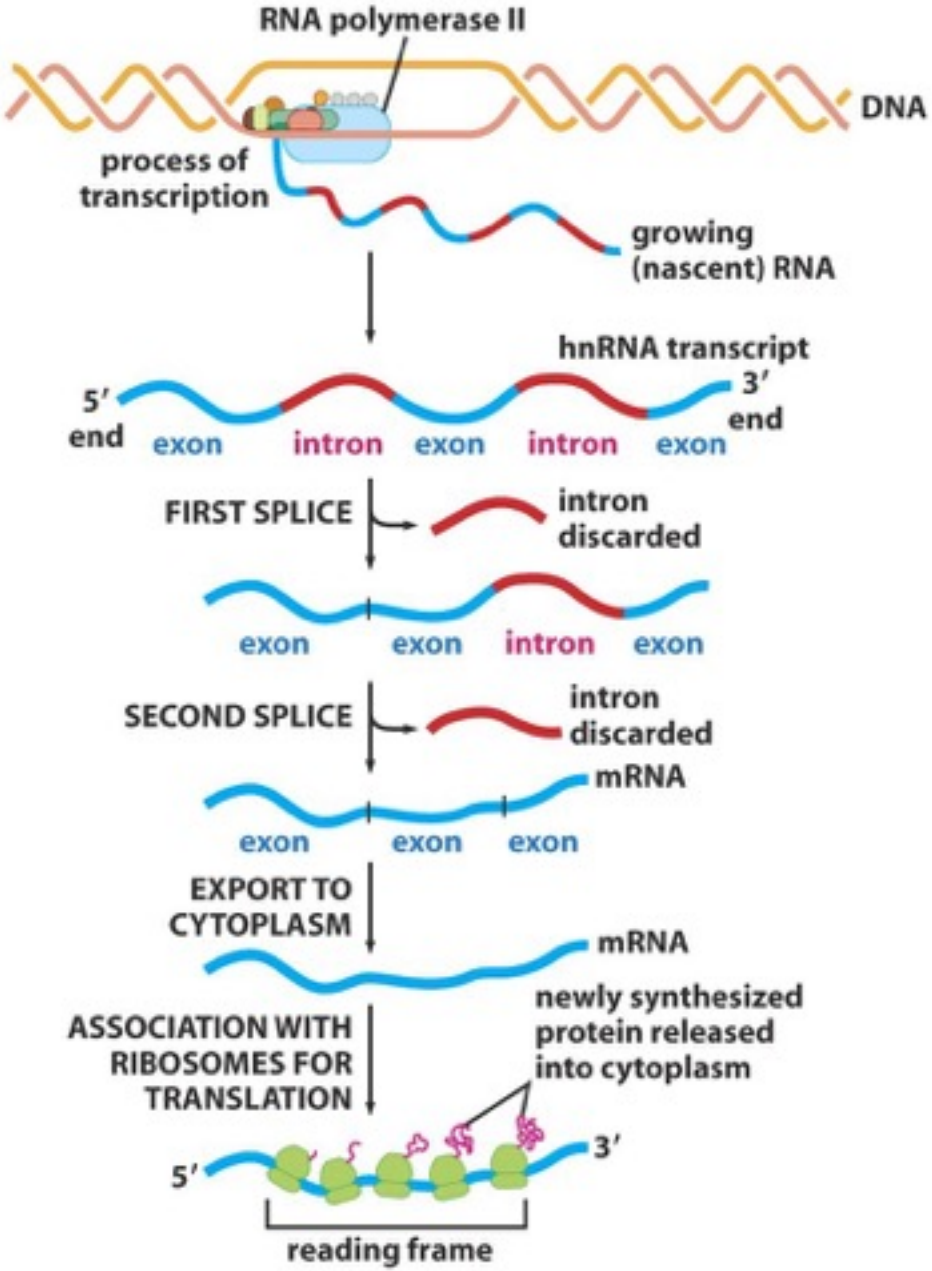
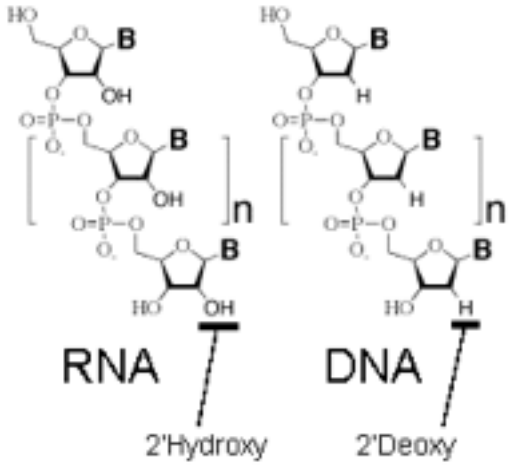


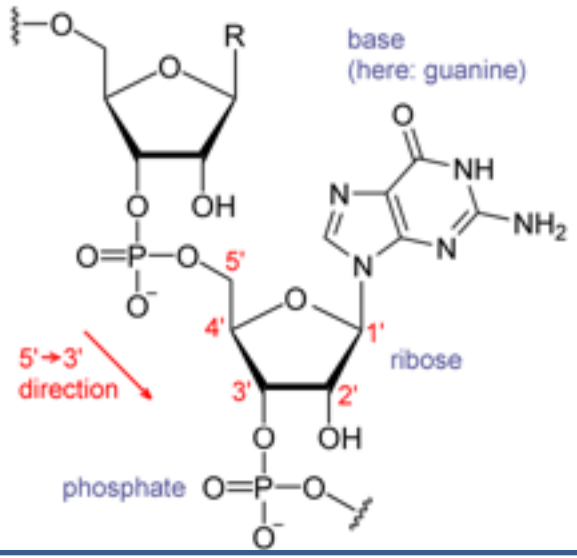
Figure 1-17a The Biology of Cancer (© Garland Science 2007)

RNA (Ribonucleic Acid) vs DNA

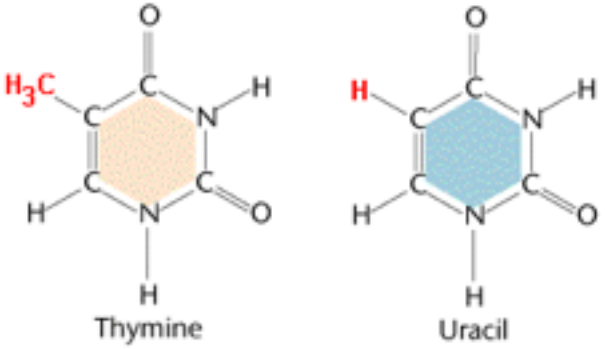


http://scienceblogs.com/transcript/2006/11/autism_rna.php

Ribose sugar (vs deoxyribose)



Uracil instead of Thymine



(Klug & Cummings 1997)

http://www.mun.ca/biology/scarr/T_versus_U.html

WHAT DOES TRANSCRIPTION NEED?

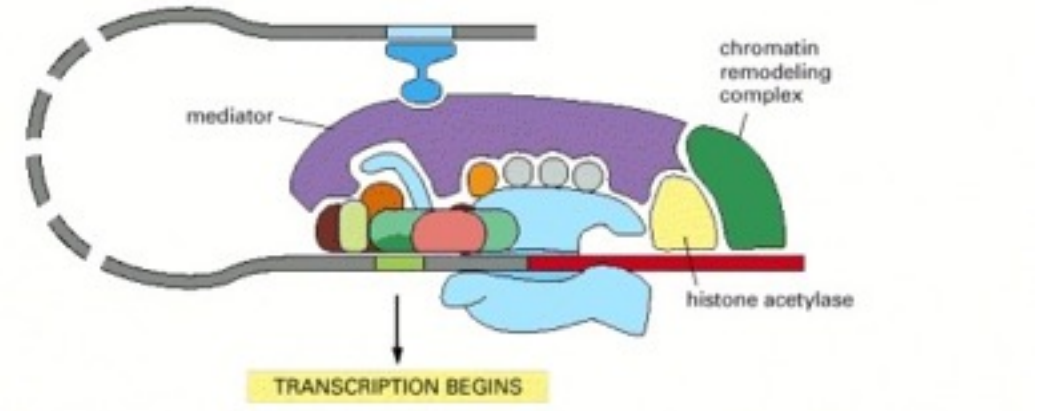
- Promoter (enhancers/silencers)
- TSS
- RNA Polymerase II
- Regulatory complexes
- Histone modifications
- DNA methylation status (Dr. Smiraglia)

PROMOTER

- DNA region upstream the **TSS** (Transcriptional Start Site)
- Can be tens of kbs long
- Contains **enhancers** (that bind *CoActivator* proteins) and **silencers** (that bind *CoRepressor* proteins)
- **TATA box binding site** to prime TFs and PolII binding

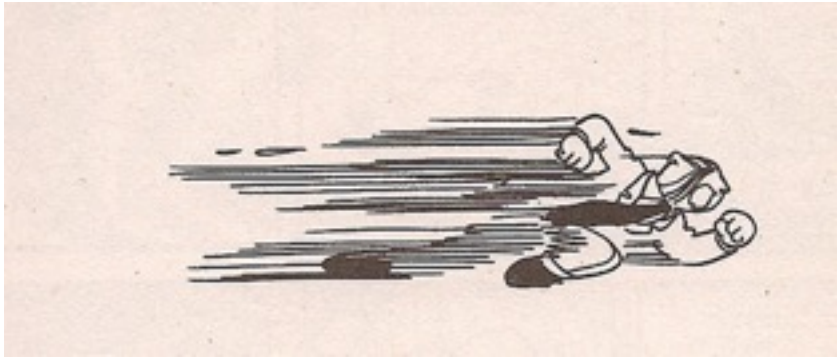
TSS AND INITIATION COMPLEX

- Chromatin structure is “open” to allow transcriptional complex to access DNA
- TATA Binding protein (TBP – TFIID subunit), DNA Helicase 4, TFIIA/B/E/F/H and PolII bind to the promoter
- Mediator complex “bridges” between distal sites to connect different TFs

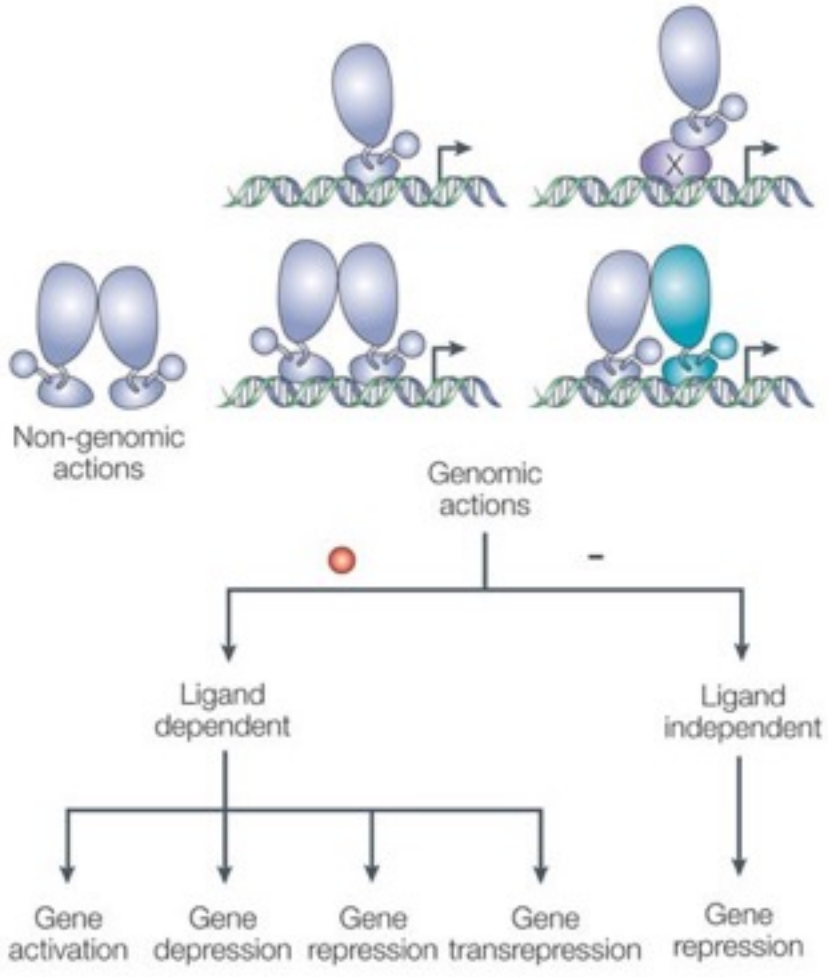


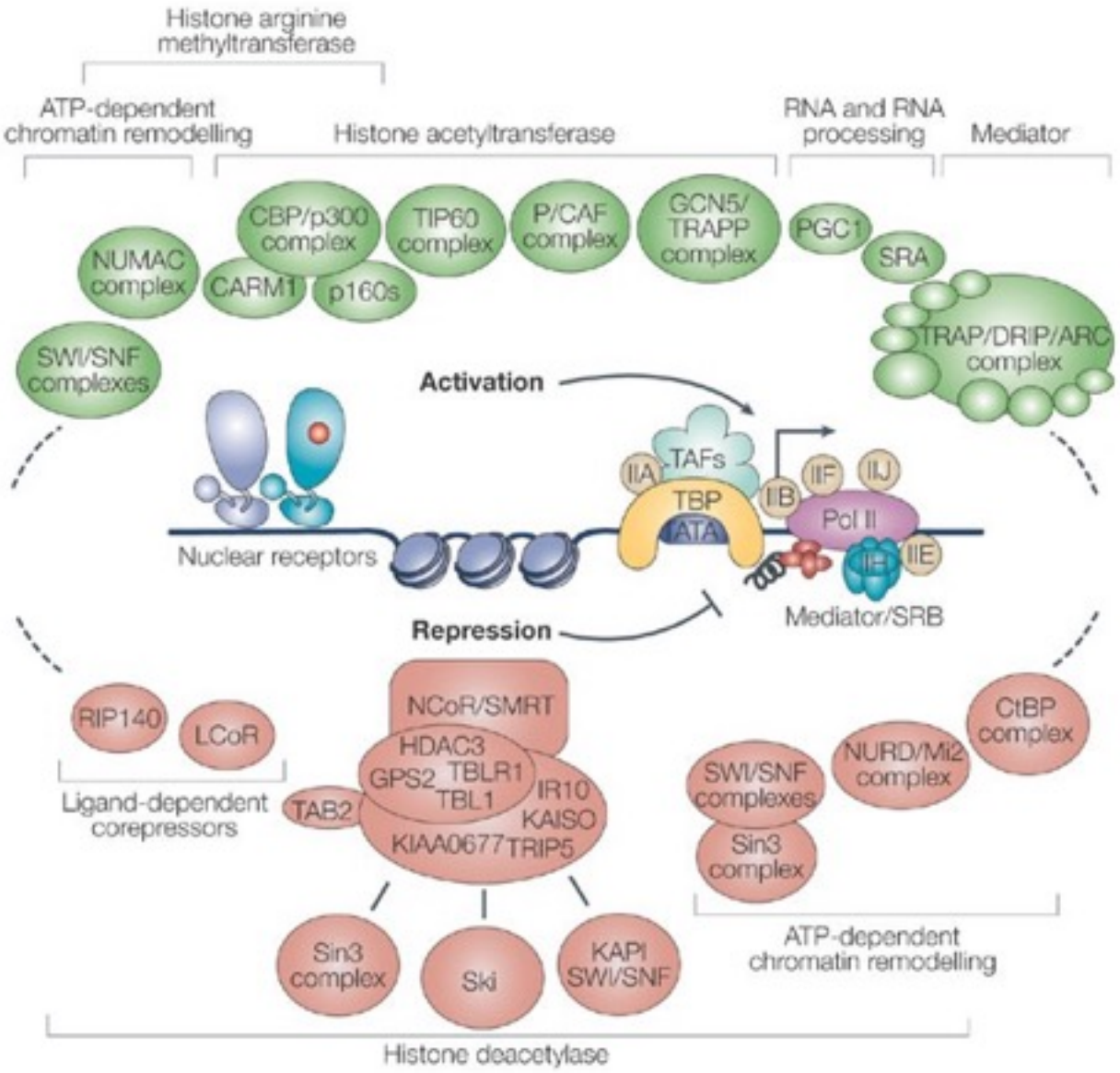
Molecular Biology of the Cell. 4th edition.
Alberts B, Johnson A, Lewis J, et al.

- Once transcription starts several PolII can transcribe the same gene
- Elongation occurs at a speed of 1000-4000bp/ min
- Proofreading mechanism in RNA synthesis too
- The end of the transcript is formed by a 5’ Poly-A tail (~25nt)

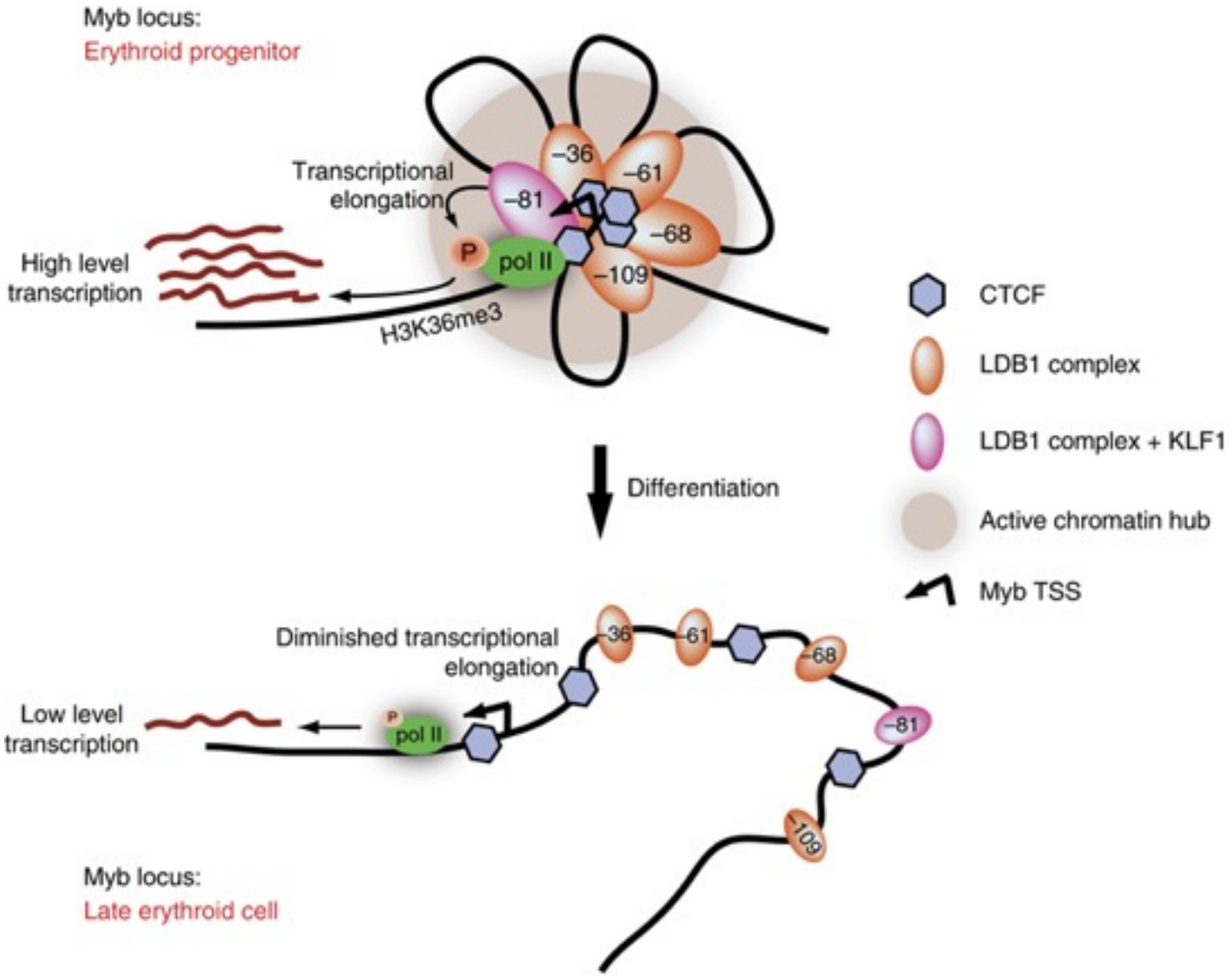


TRANSCRIPTION FACTORS

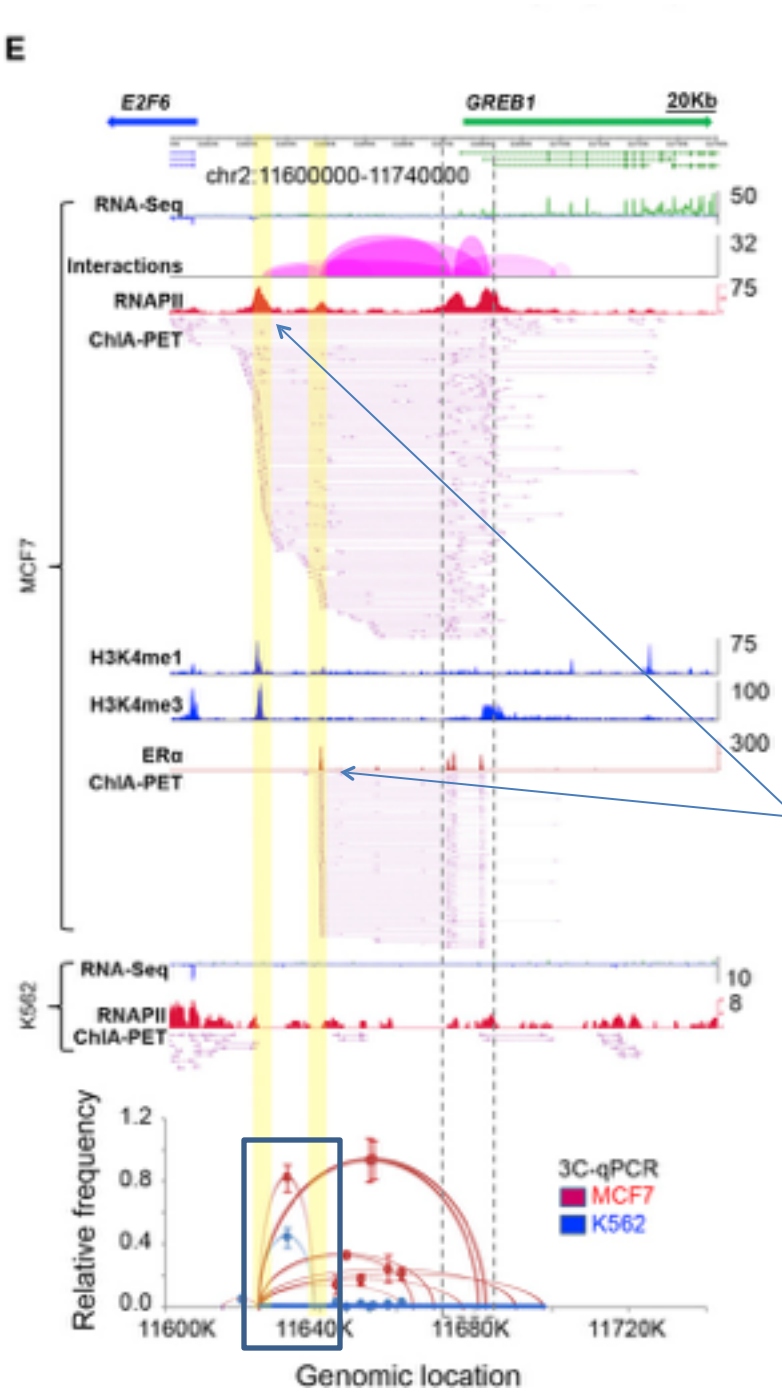




Nature Reviews | Molecular Cell Biology



The EMBO Journal (2012) **31**, 986 - 999



Long range chromatin interactions are heavily implicated in transcriptional regulation.

MCF-7 (breast cancer) –specific interaction around the GREB1 locus.

pPol-II interactions with distal ER-binding sites evaluated via ChIA-PET and 3C assay.

TRANSCRIPTION AND CANCER

- Transcription is finely regulated by regulatory complexes
- ***THERE IS A FINE EQUILIBRIOUM BETWEEN TRANSCRIPTIONAL ACTIVATION AND REPRESSION***

- Loss of this equilibrium can lead to inactivation of tumor suppressor genes or constitutive activation of oncogenes

TRANSCRIPTION AND CANCER

- Epigenetic events:
  - Histone modifications
  - DNA methylation
  - miRNAs
- Overexpression/Downregulation of CoActivators or CoRepressors
- Mutations at the promoter region (i.e. in binding regions for TFs)

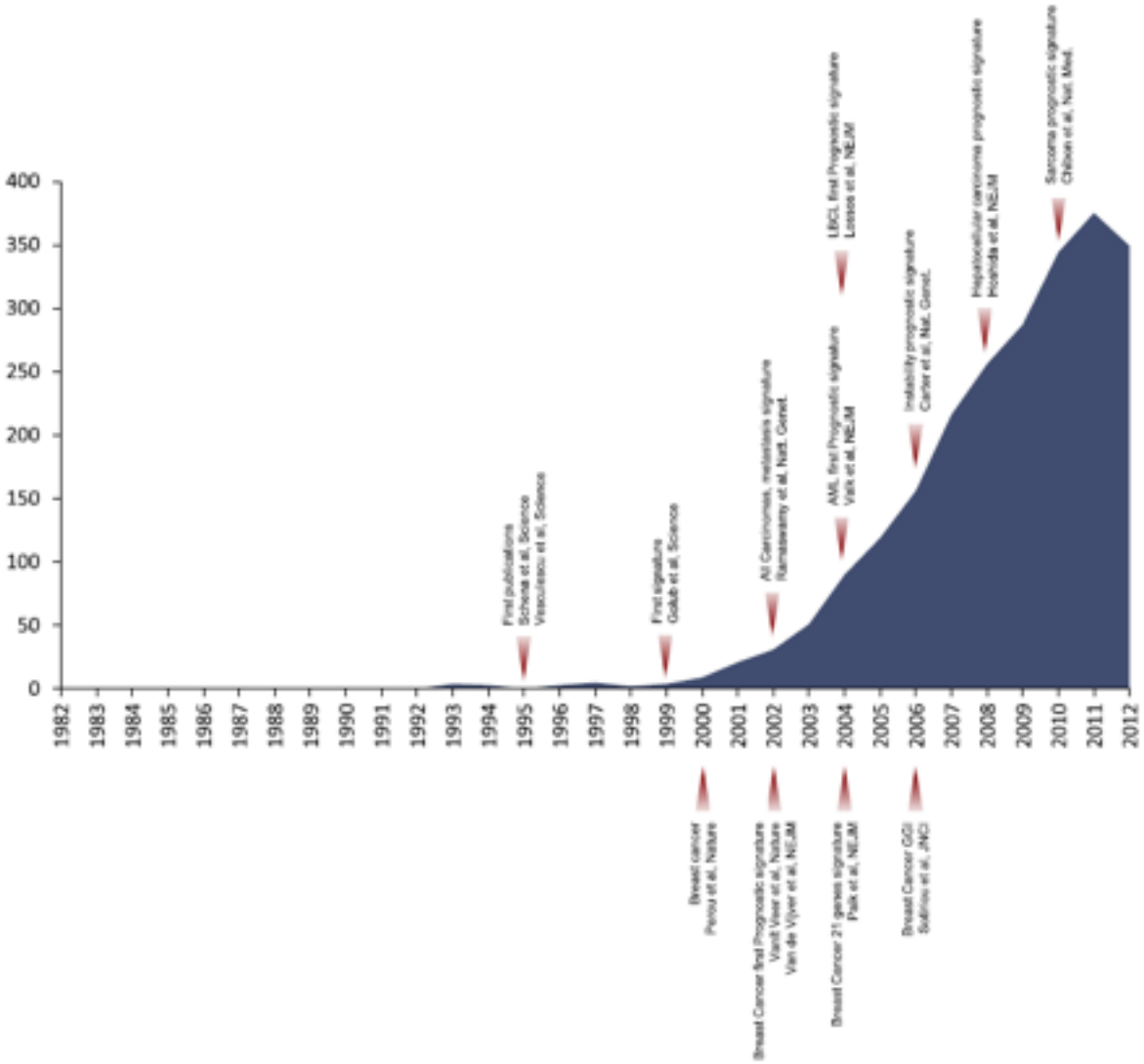
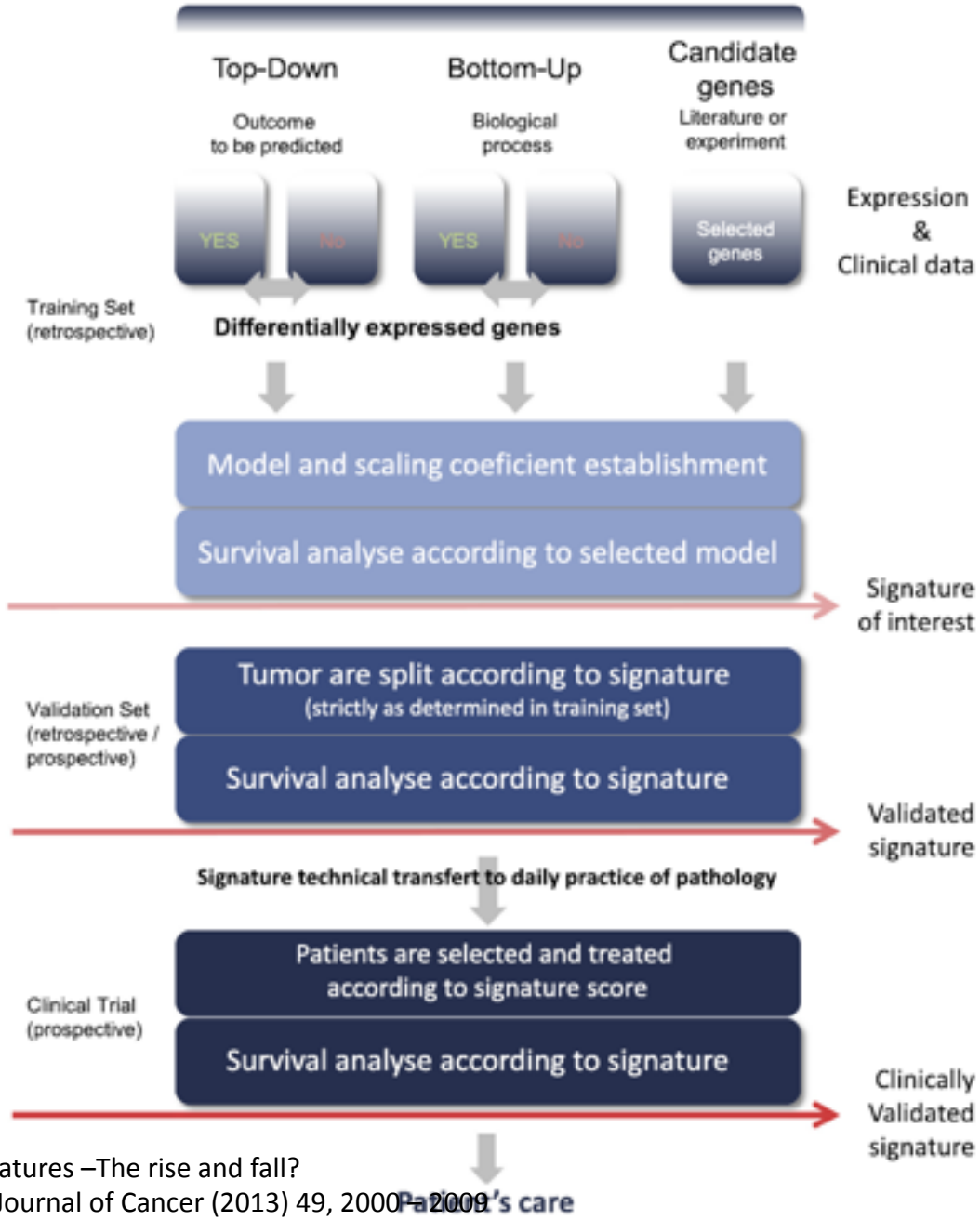
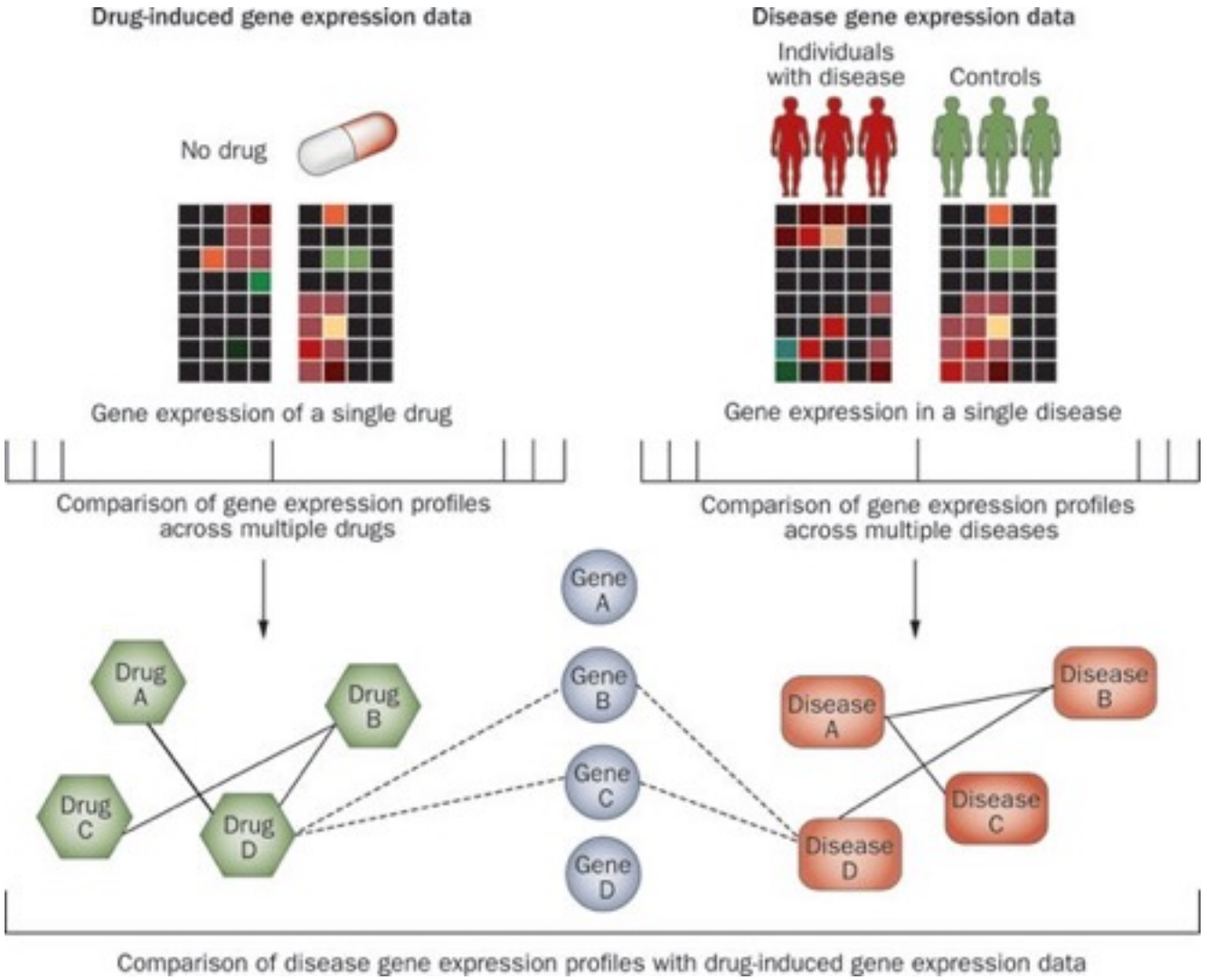


Fig. 1. Number of results (*Y*-axis) for the PubMed query: 'cancer gene expression signature' per year (*X*-axis). Red arrows indicate the year of some of the main publications in the field.

Cancer gene expression signatures –The rise and fall?
Frederic Chibon - European Journal of Cancer (2013) 49, 2000 – 2009

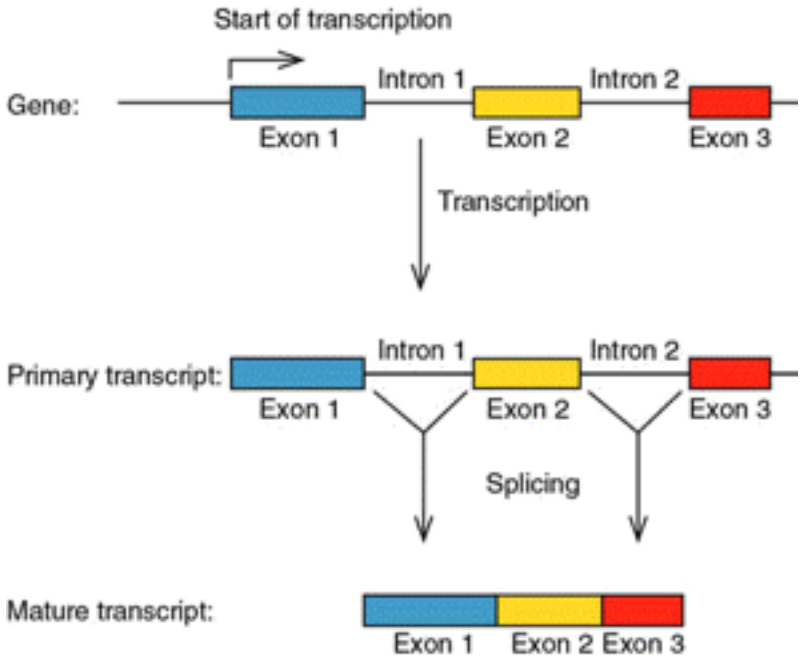


Cancer gene expression signatures –The rise and fall?
Frederic Chibon - European Journal of Cancer (2013) 49, 2000–2009



The role of bioinformatics in studying rheumatic and autoimmune disorders
Marina Sirota & Atul J. Butte
Nature Reviews Rheumatology 7, 489-494 (August 2011)

RNA SPLICING



alpha-tropomyosin

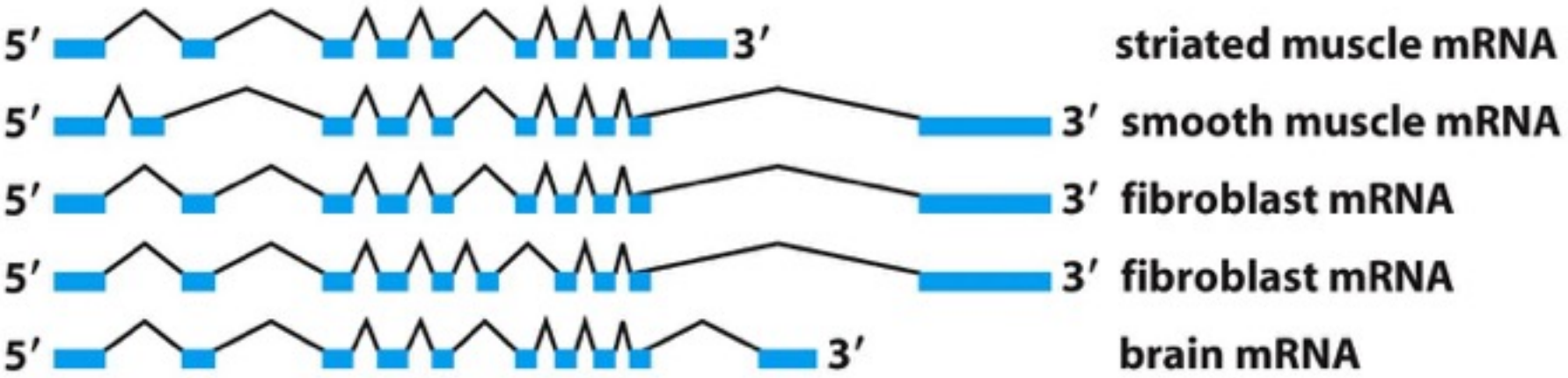
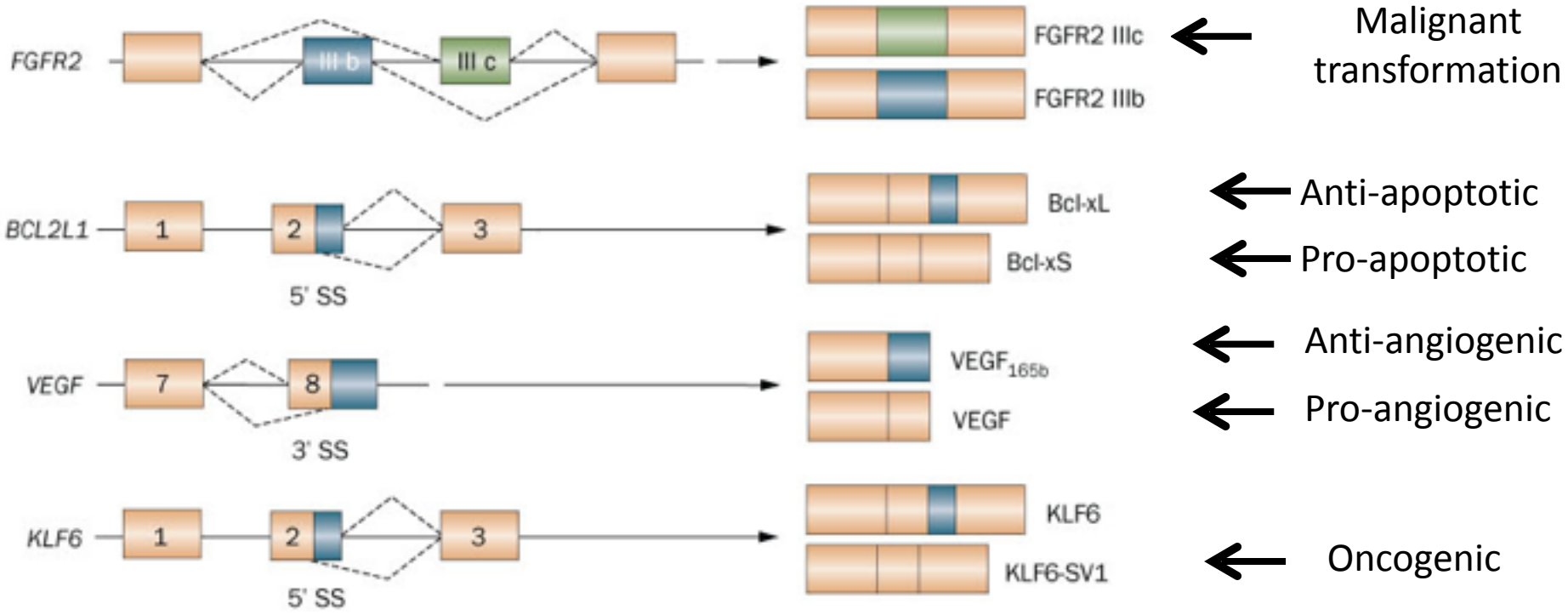


Figure 1-17b The Biology of Cancer (© Garland Science 2007)

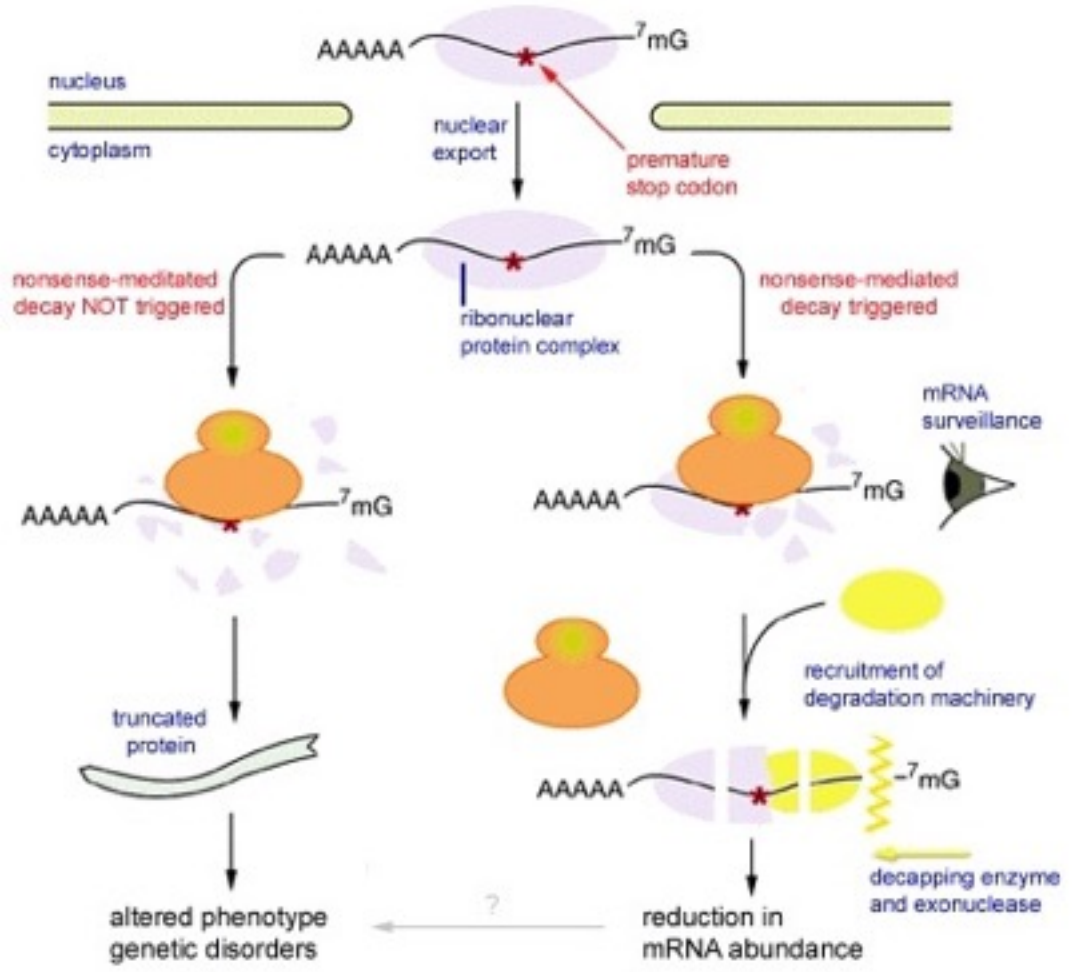
ALTERNATIVE SPLICING IN PCa



Nat Rev Urol. 2009 Aug;6(8):454-60.
Alternative splicing and biological heterogeneity in prostate cancer.
Rajan P, Elliott DJ, Robson CN, Leung HY.

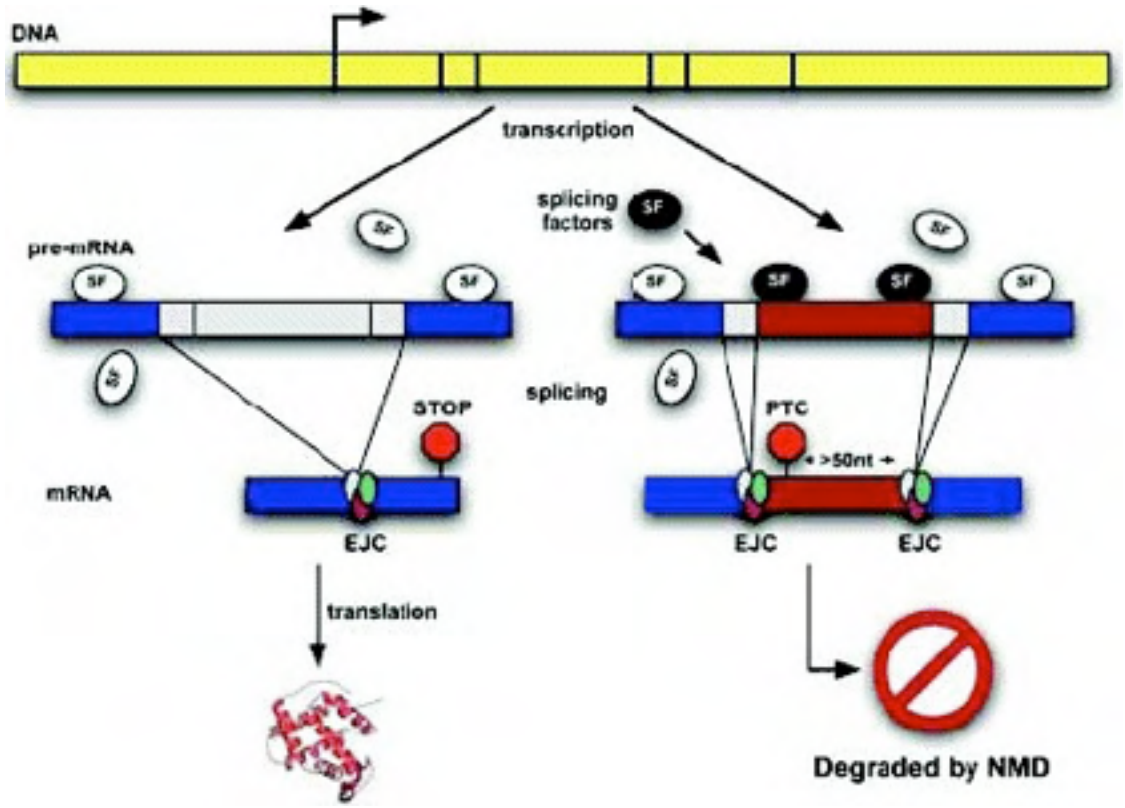
NMD – Nonsense Mediated Decay

- mRNA surveillance mechanism
- **Detects nonsense mutations preventing translation of truncated proteins**
- NMD helps maintaining proper levels of gene expression



NCBI Bookshelf

RNA surveillance: watching the defectives detecting premature stop codons in mRNA halts the production of dangerous truncated proteins



Exon Junction Complex (EJC) binds 20-24nt upstream of each exon-exon junction

Pioneer round of translation

If nonsense codon (NC) detected 50-55nt upstream od EJC → mRNA degraded

If NC closer than 50-55nt to EJC or downstream → no NMD

Examples of notable Mutations

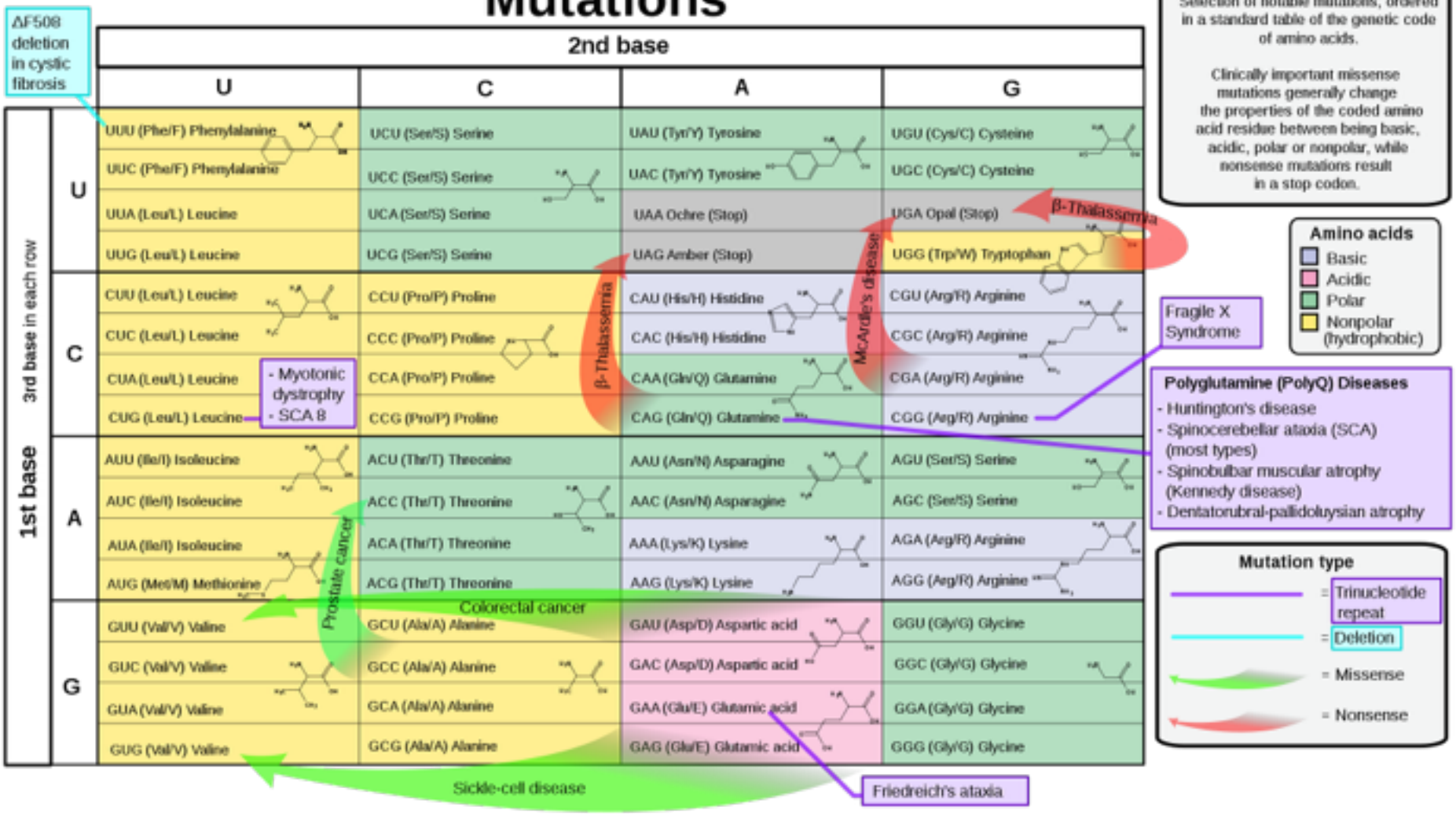
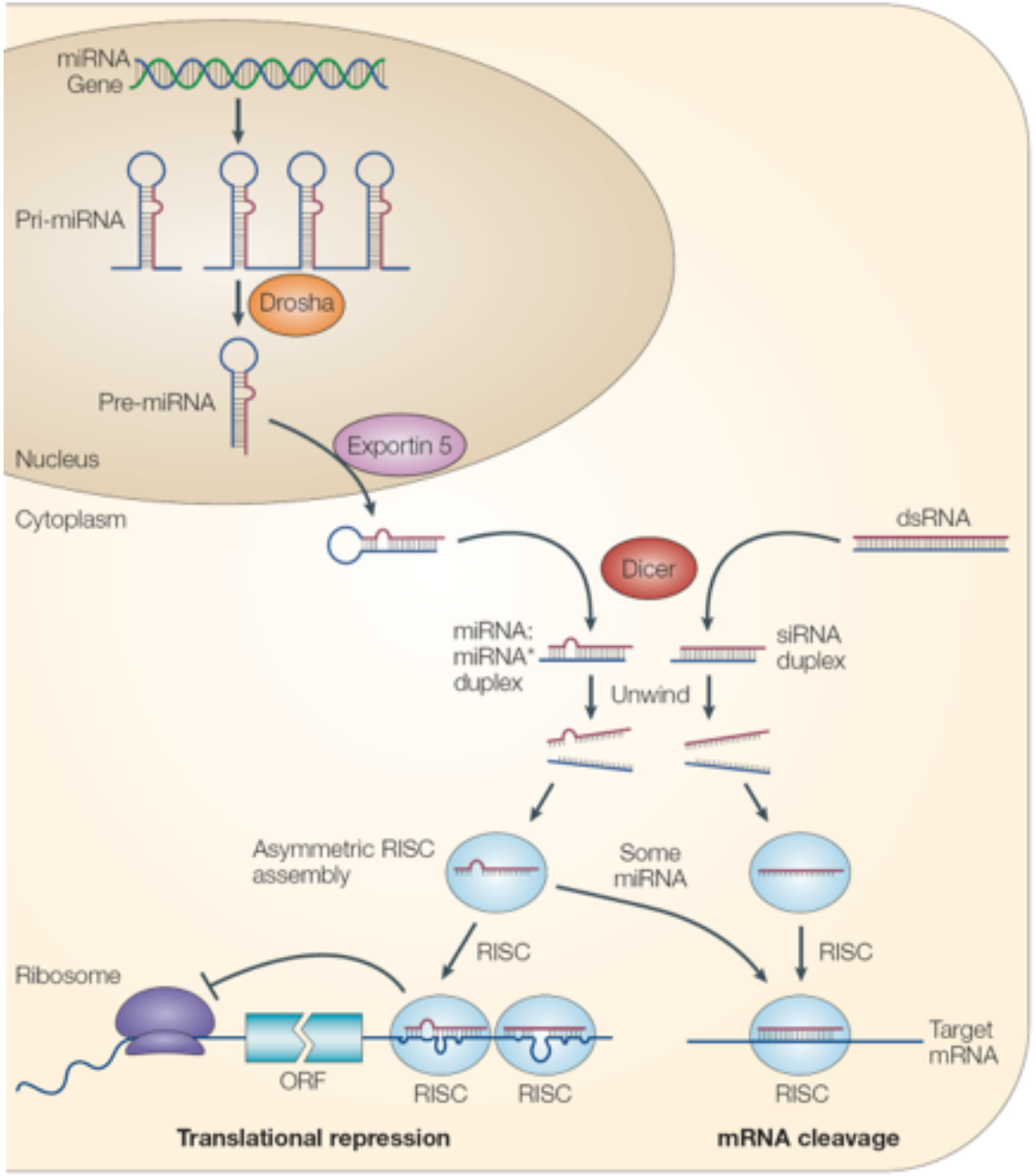


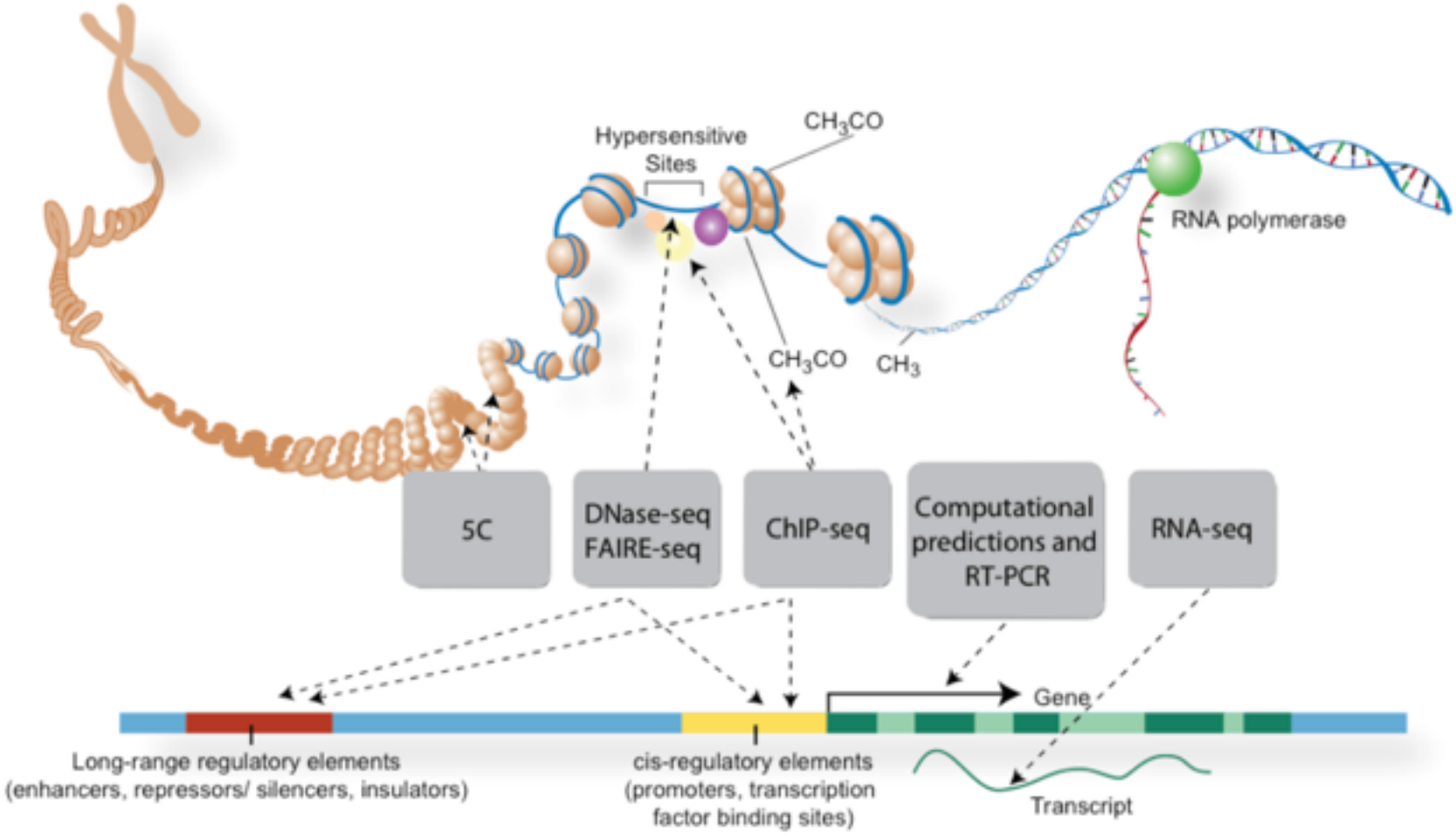
Image created by: **Mikael Häggström** - Wikipedia

miRNAs



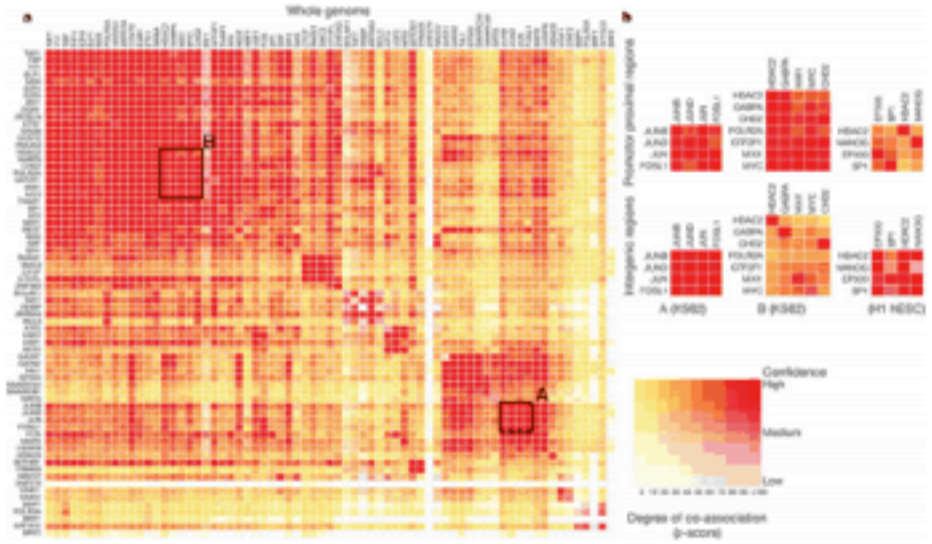
MicroRNAs: small RNAs with a big role in gene regulation
Lin He & Gregory J. Hannon
Nature Reviews Genetics 5, 522-531 (July 2004)

ENCODE PROJECT



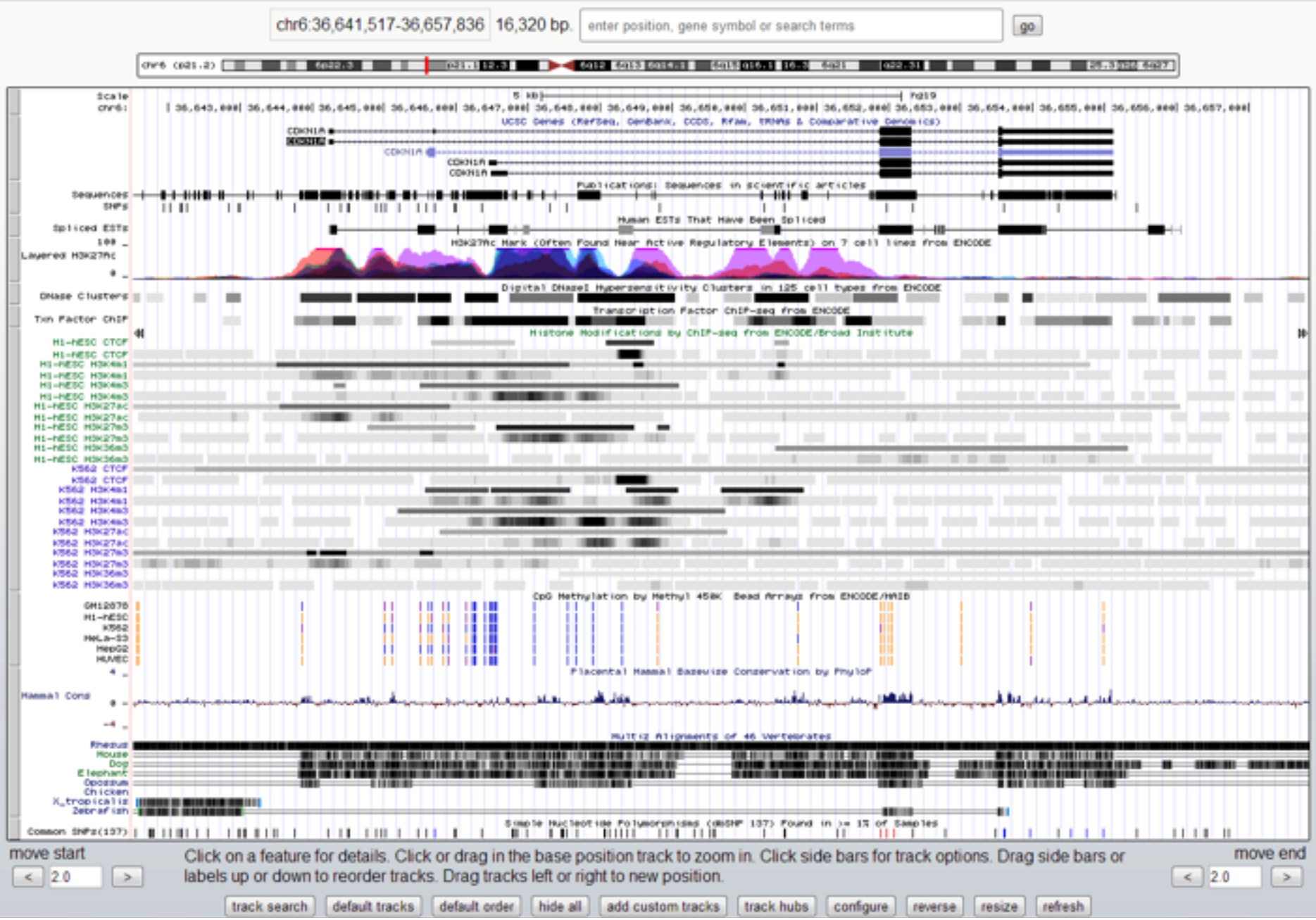
http://genome-mirror.duhs.duke.edu/ENCODE/

Co-association between transcription factors.

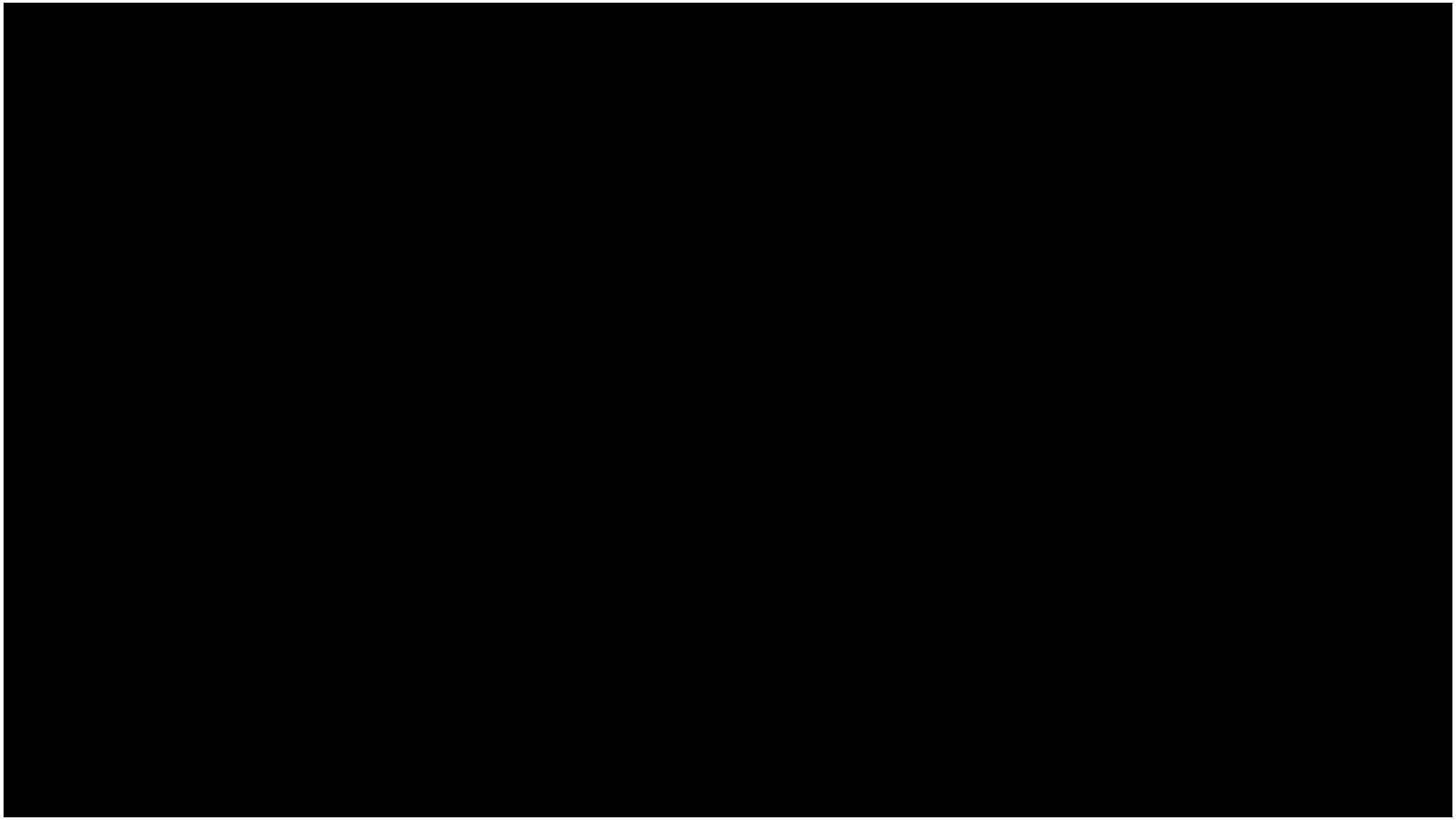


I Dunham *et al. Nature* **000**, 1-18 (2012) doi:10.1038/nature11247

nature


chr6:36,641,517-36,657,836
16,320 bp.
enter position, gene symbol or search terms
go
move start
move end
Click on a feature for details. Click or drag in the base position track to zoom in. Click side bars for track options. Drag side bars or labels up or down to reorder tracks. Drag tracks left or right to new position.
track search
default tracks
default order
hide all
add custom tracks
track hubs
configure
reverse
resize
refresh

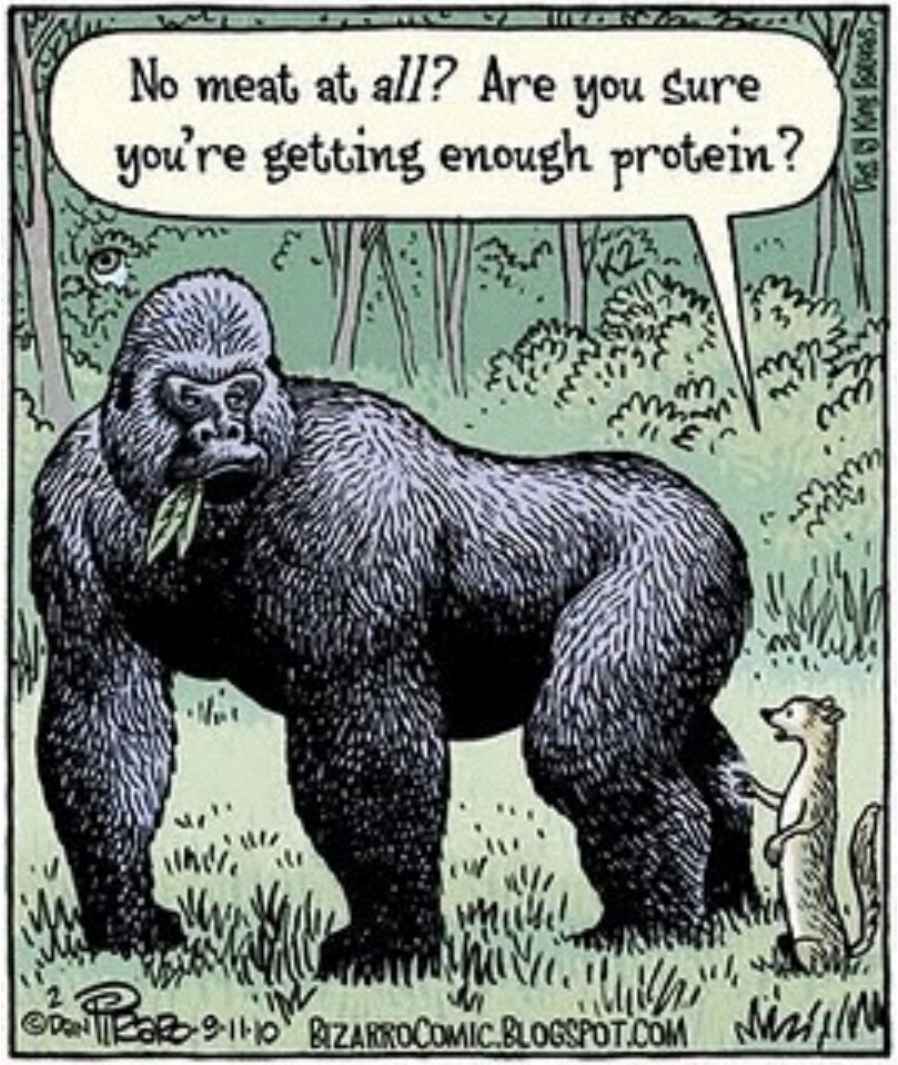
ENCODE project



SO….

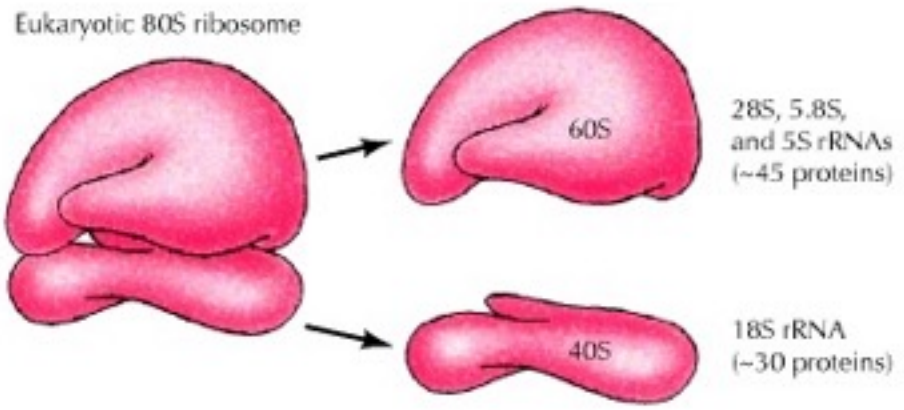
- RNA-PolII, together with a cohort of TFs, synthetizes the RNA molecule
- RNA splicing produces the final template for translation, splicing defects can lead to cancer
- Perfectly functioning transcriptional machinery is key for healthy cells
- Loss of the equilibrium between transcriptional activation/repression can lead to cancer

PART 3
TRANSLATION



RIBOSOMES

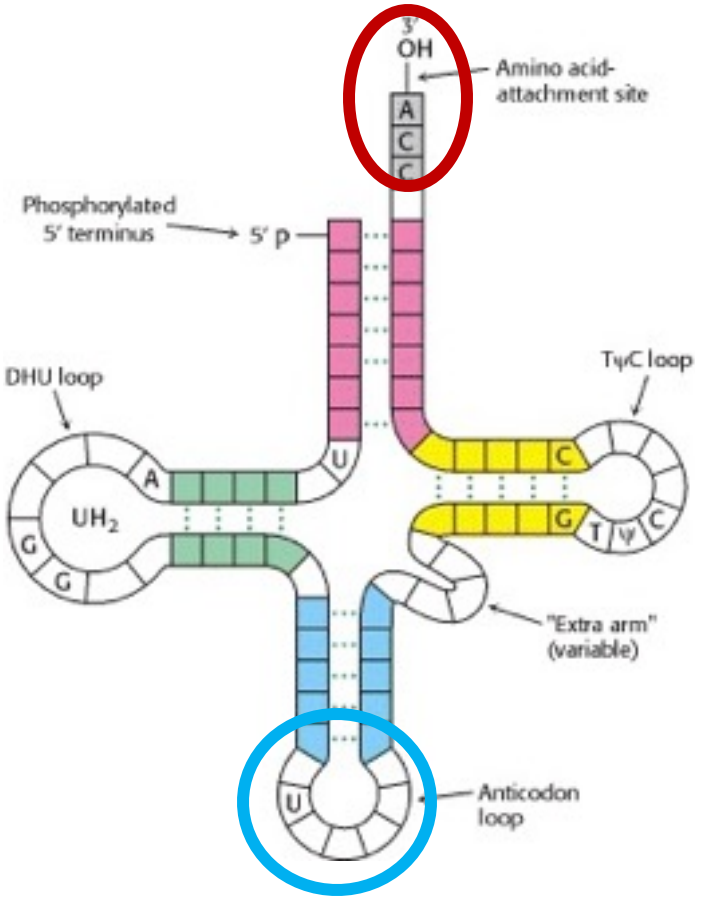
- Process that “reads” the mRNA molecule and translates it into aa sequence to create proteins
- Ribosomes are the “factories” where proteins are created

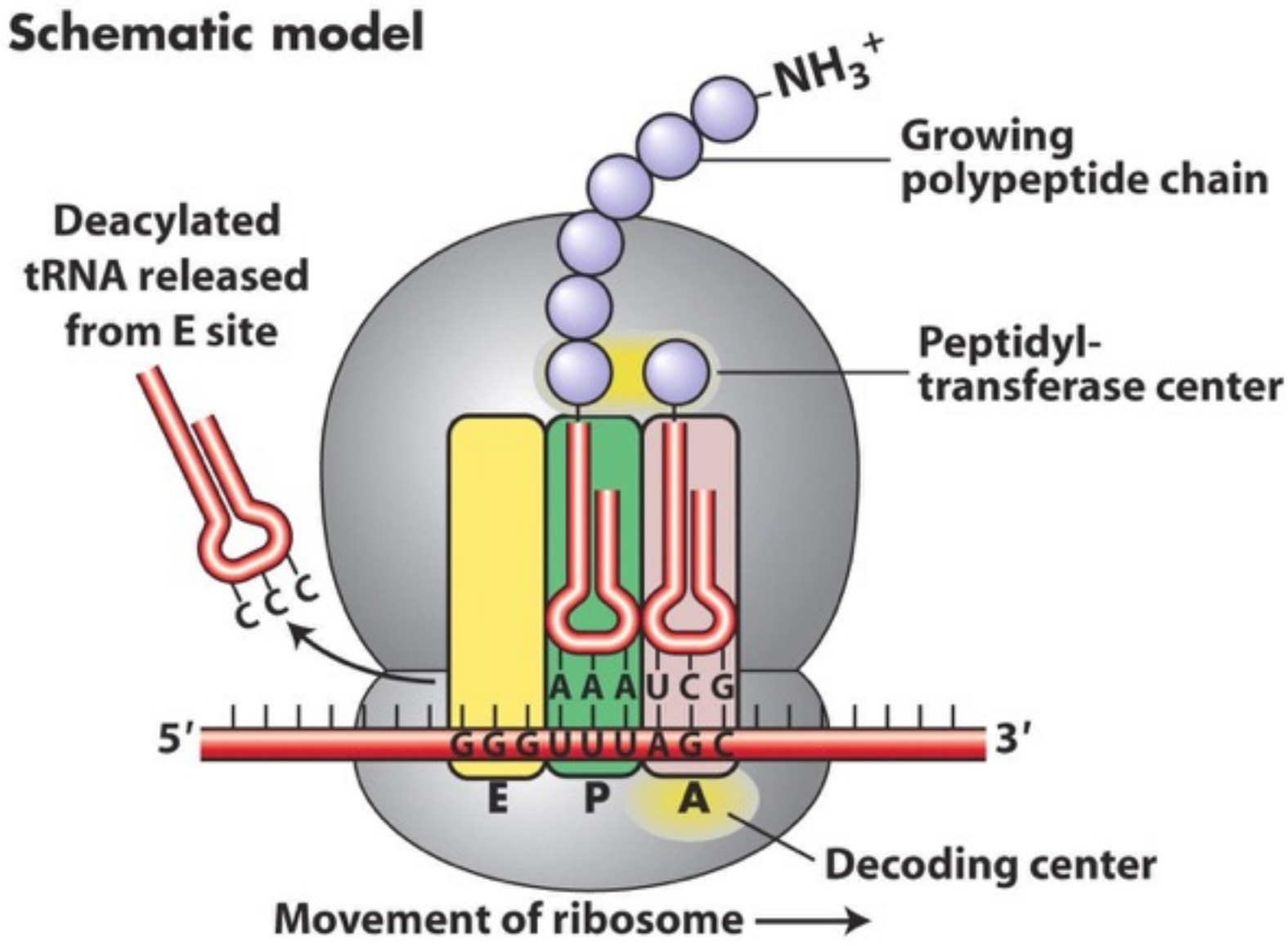


The Cell: A Molecular Approach. 2nd edition.
Cooper GM.

TRANSFER RNA - tRNA

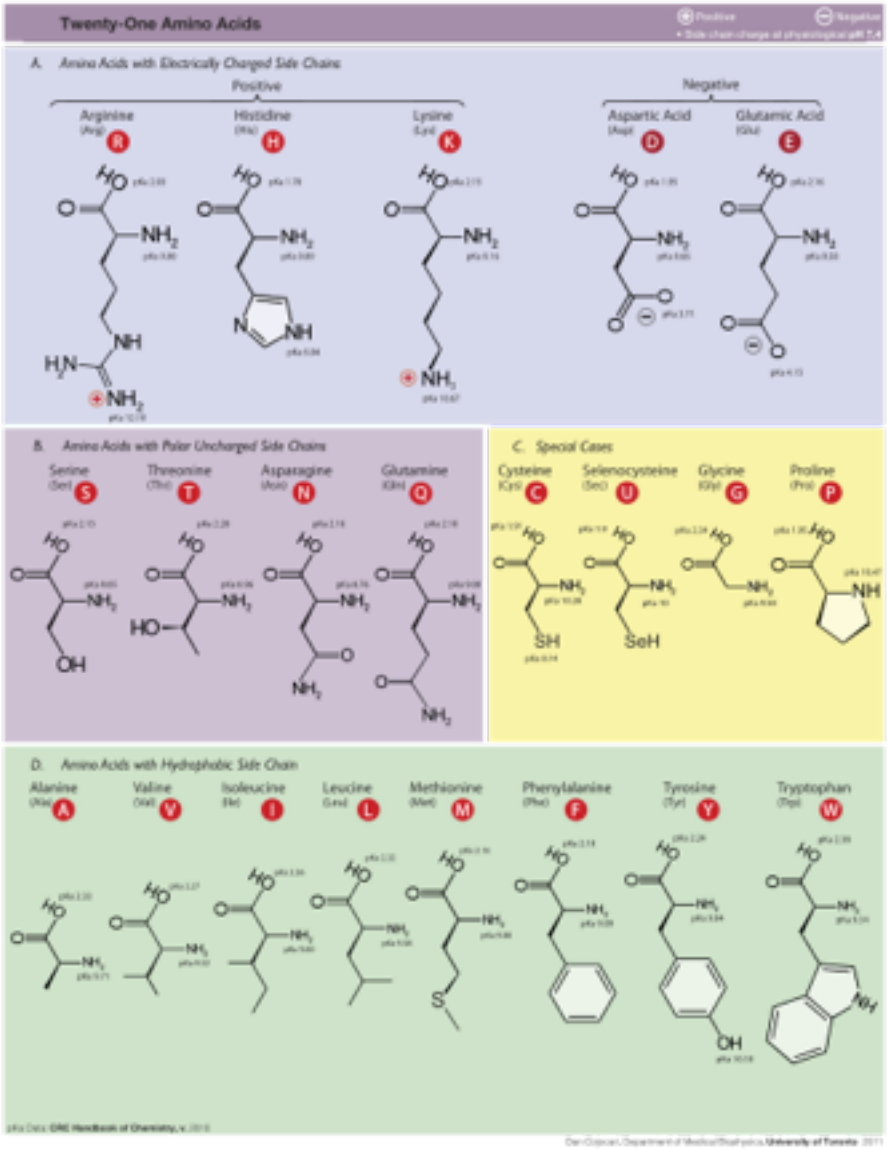
- tRNAs are 70-80nt long
- Aminiacil tRNA synthetase binds the aa to the tRNA
- Anticodon loop complementary to the mRNA sequence




Schematic model
NH_3^+
Growing polypeptide chain
Deacylated tRNA released from E site
Peptidyl-transferase center
C C C
A A A U C G
5′
G G G U U U A G C
3′
E
P
A
Decoding center
Movement of ribosome

DEGENERATE CODE

	U	C	A	G
U	UUU Phe UUC UUA Leu UUG	UCU UCC UCA UCG Ser	UAU Tyr UAC UAA Stop UAG	UGU Cys UGC UGA Stop UGG Trp
C	CUU CUC CUA CUG Leu	CCU CCC CCA CCG Pro	CAU His CAC CAA Gln CAG	CGU CGC CGA CGG Arg
A	AUU AUC AUA Ile AUG Met	ACU ACC ACA ACG Thr	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG
G	GUU GUC GUA GUG Val	GCU GCC GCA GCG Ala	GAU Asp GAC GAA Glu GAG	GGU GGC GGA GGG Gly

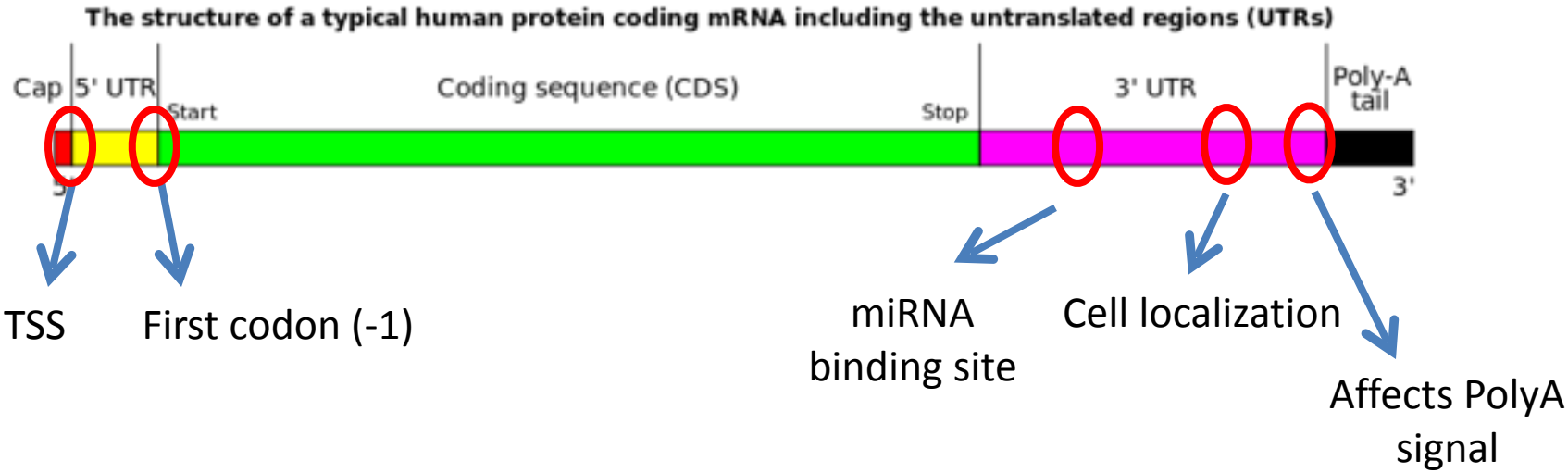


aa read from 3pbs

4bp x 4bp x 4pb = 64 possible aa

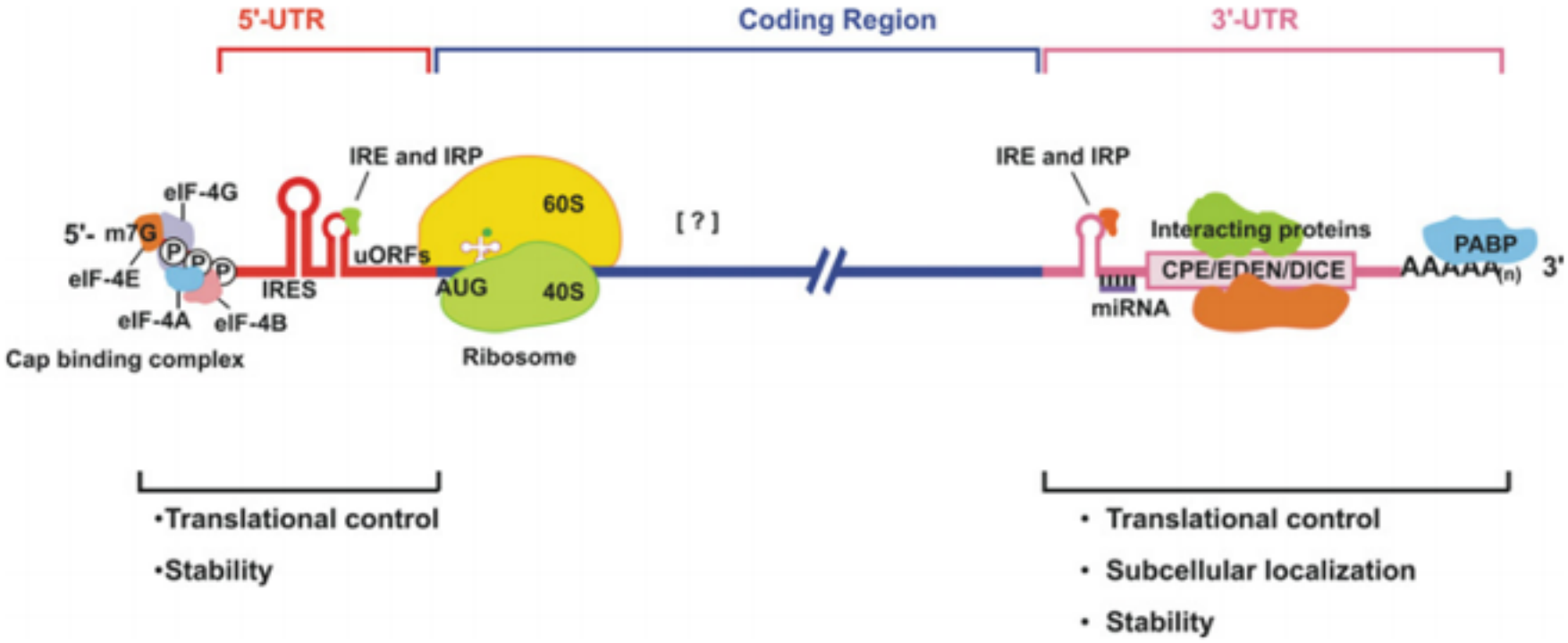
But…only 20 obtained from the genetic code…

5’UTR – 3’UTR



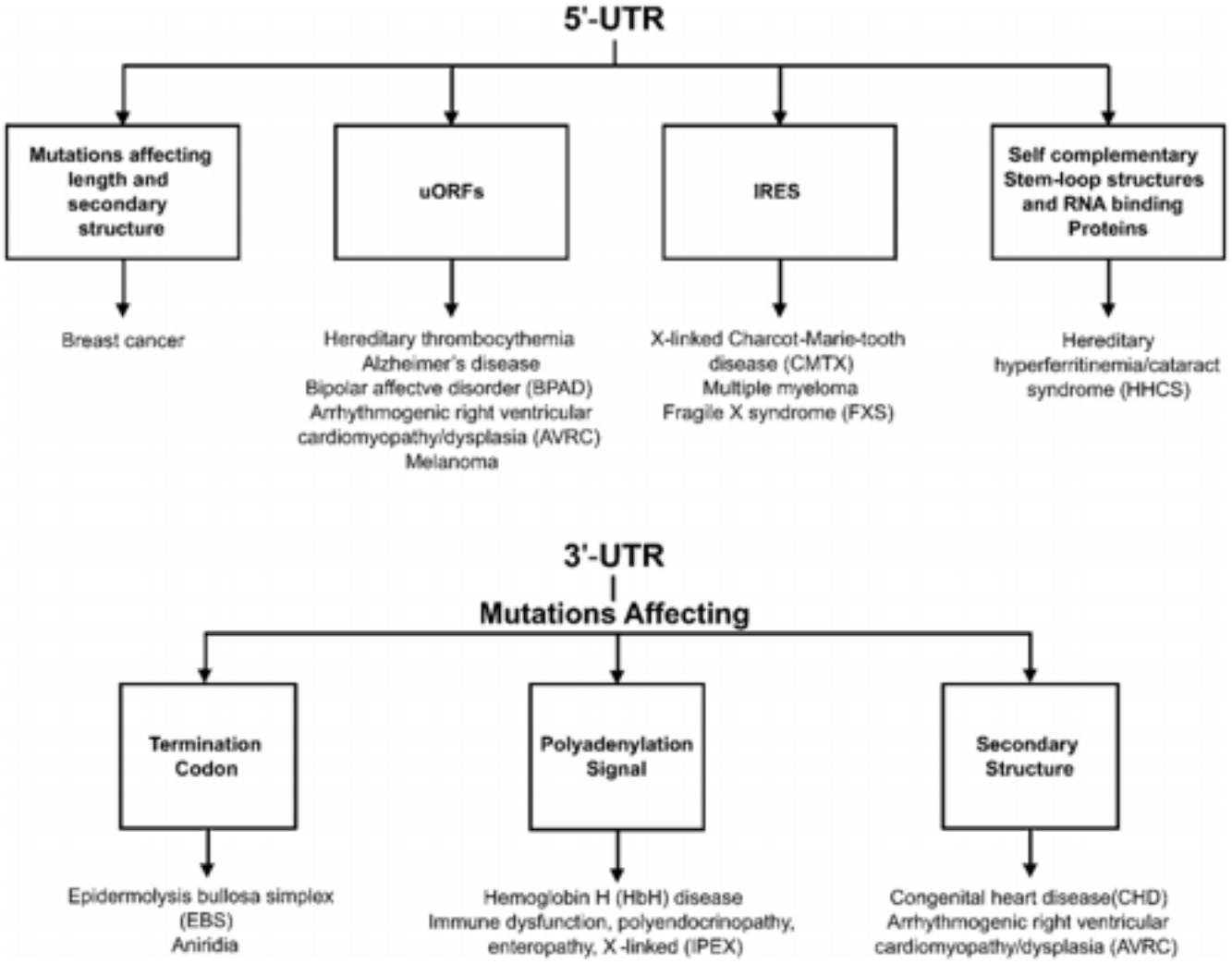
- Control mRNA stability
- Contain regulatory regions and protein binding sites

- Length: ~200-2000bp long
- GC content affecting thermal stability
- Presence of intact IRES (Internal Ribosome Entry Site) for binding to 40s
- Secondary structure
- Mutations



Biol. Cell (2009) 101, 251–262
Role of 5'- and 3'-untranslated regions of mRNAs in human diseases
Sangeeta Chatterjee and Jayanta K. Pal

Figure 2 | Involvement of various regulatory elements of 5′- and 3′-UTRs of mRNAs in various diseases



Biol. Cell (2009) 101, 251–262
Role of 5′- and 3′-untranslated regions of mRNAs in human diseases
Sangeeta Chatterjee and Jayanta K. Pal

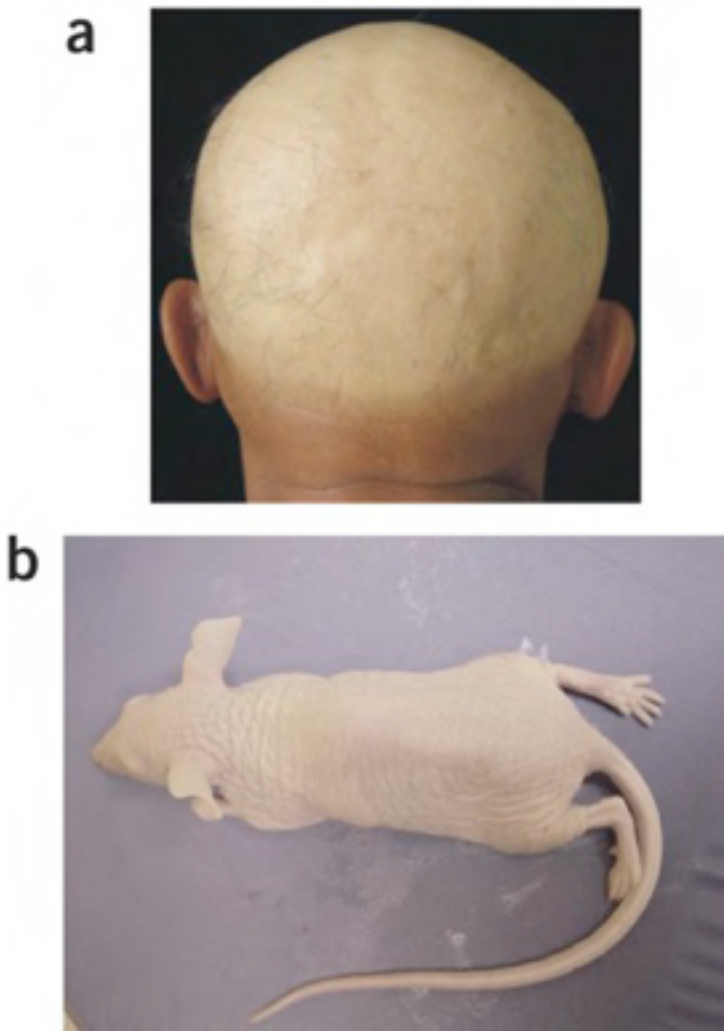
UPSTREAM ORF (uORF)

- Present in many eukaryotic genes, generally short and juxtaposed to the actual ORF (open reading frame).

- uORFs control translation mainly by:
  - sequestering ribosomes that dissociate prematurely at the stop codon and may or may not re-initiate translation at a downstrem ORF
  - Inducing NMD

- Mutation of an existing uORF will lead to aberrant translation/ upregulation while mutations introducing a new uORF will aberrantly decrease translation (like observed for CDKN2A in some patients predisposed to melanoma).

UPSTREAM ORF (uORF)



Nearly complete alopecia observed in an individual with Marie Unna hereditary hypotrichosis (MUHH), caused by mutations in an upstream open reading frame (uORF) flanking the hairless (Hr) gene.

Lorin Weiner & Janice L Brissette
Nature Genetics 41, 141 - 142
(2009)

SO…

- mRNA is translated to proteins following a strict code
- Rate of translation is regulated by *cis*-elements and *trans*-acting proteins
- Deregulation of translation can lead to several diseases and increased cancer susceptibility

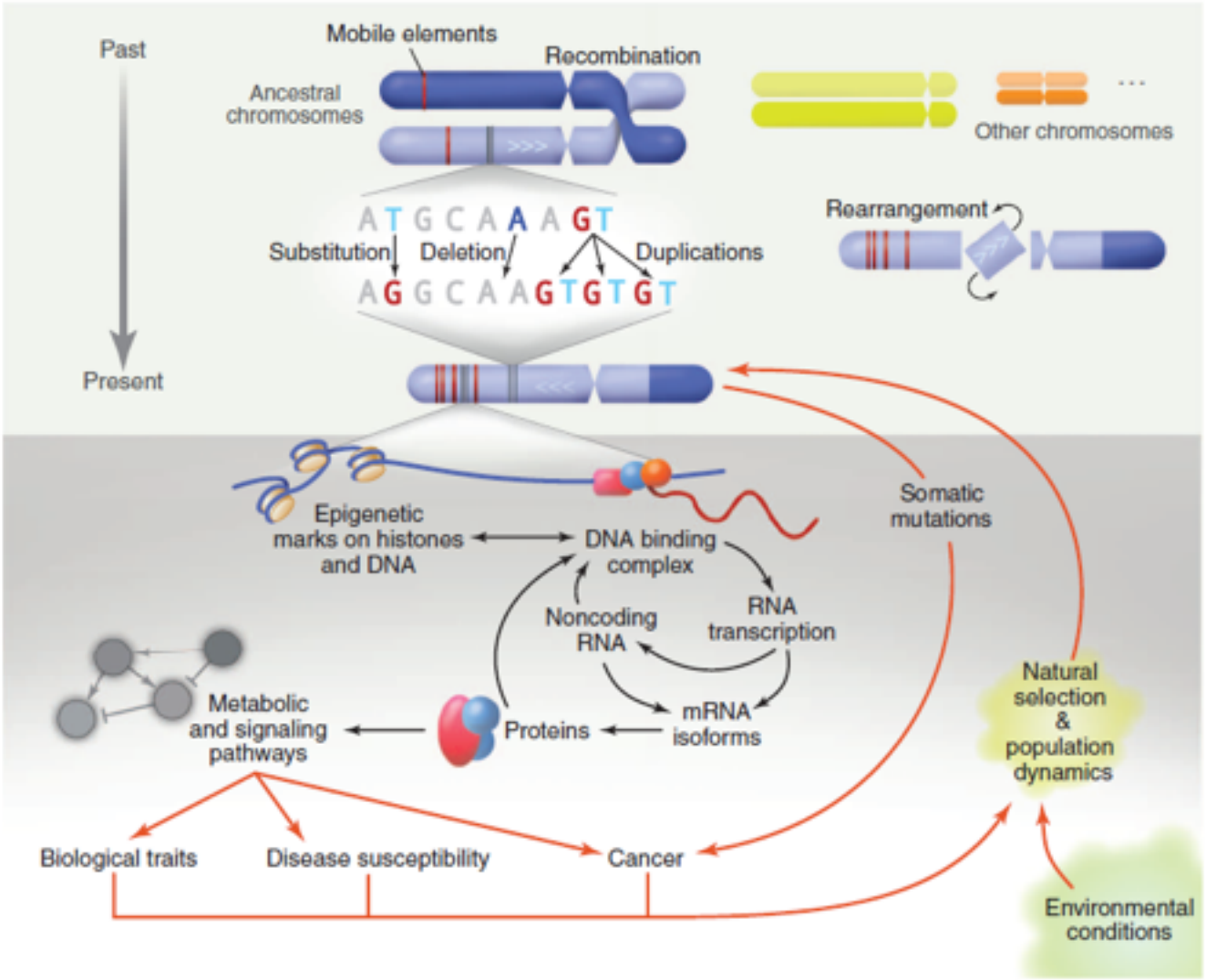
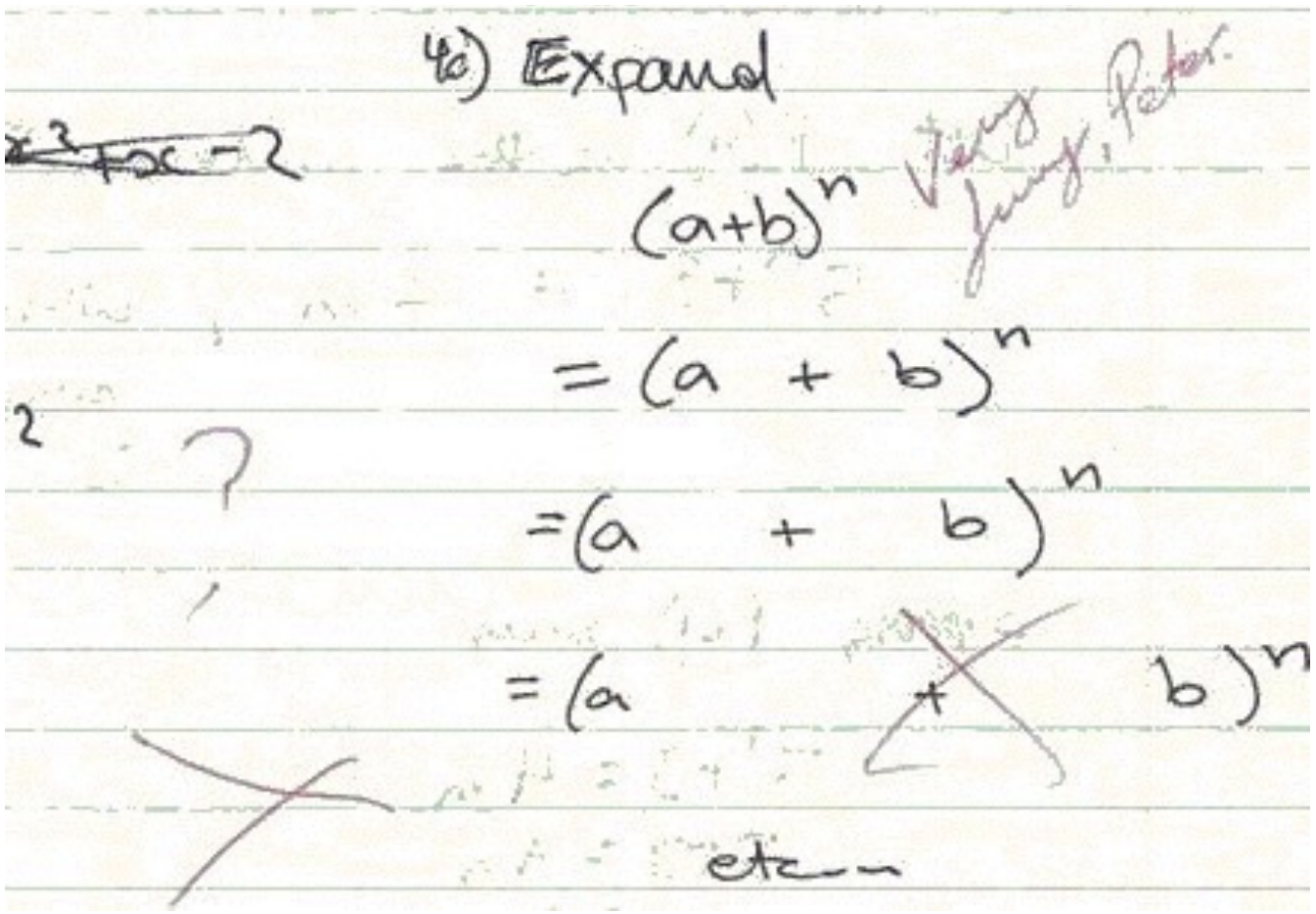


Fig. 2. The dynamic processes that affect and are affected by the genome. **Top**: The genome changes as it is modified by random mutations. At the larger scale, homologous recombination events swap equivalent pieces of DNA, rearrangements reconnect different regions of DNA, and transposable elements can self-reproduce. At the finer scale, small modifications such as substitutions and insertion/deletion events occur. **Bottom**: The genome affects the molecular processes in the cell, namely the transcription of genes and functional RNA, which through pathways affect the phenotype of the organism by causing phenotypes such as disease and other specific traits. Through natural selection, the phenotypes condition the selective pressure on the genome favoring or disfavoring specific mutations.

QUESTIONS…?!



Sebastiano.Battaglia@roswellpark.org