Oncology for Scientists

- CHROMOSOME STRUCTURE, REPLICATION, TRANSCRIPTION, TRANSLATION -

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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

• ~ 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
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](http://micro.magnet.fsu.edu/cells/nucleus/chromatin.html)
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 \textbf{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.

• ~2.9 billions of base pairs

• ~30k genes

• 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
Mice (mTR-/−) are healthy until second and third generation, by 4th and 5th 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
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 (154-260bp).
HISTONE MODIFICATIONS

A

NUCLEOSOME  FRONT  BACK  HISTONE H4

K5 K8 K12 K16

Ac

B

Activation

Ac

Relaxed chromatin

Transcription activation complex containing HAT

Repression

Compacted chromatin

Transcription repression complex containing HDAC

HAT

HDAC
HISTONE MODIFICATIONS

Nature Reviews Genetics 3, 662-673 (September 2002)
PART 1
DNA REPLICATION

CLONING
Results may vary

icanhascheezburger.com by ©
DNA REPLICATION – CELL DIVISION

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
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 10,000 bp mismatches
- Proofread ~99% of its own mismatches → 1/10,000,000 rate errors
Point mutation in the pol-delta gene (D400A) is enough to block 3’->5” exonuclease activity and proofreading activity.
Set of enzymes that monitor the newly synthetized DNA to detect miscopied DNA sequences.
XERODERMA PIGMENTOSUM (XP)

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

- 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

<table>
<thead>
<tr>
<th>Name of syndrome</th>
<th>Name of gene</th>
<th>Cancer phenotype</th>
<th>Enzyme or process affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNPCC</td>
<td>(4–5 genes)*</td>
<td>colonic polyposis</td>
<td>mismatch repair enzymes</td>
</tr>
<tr>
<td>XPb</td>
<td>(8 genes)b</td>
<td>UV-induced skin cancers</td>
<td>nucleotide-excision repair</td>
</tr>
<tr>
<td>ATc</td>
<td>ATM</td>
<td>leukemia, lymphoma</td>
<td>response to dsDNA breaks</td>
</tr>
<tr>
<td>AT-like disorderc</td>
<td>MRE11</td>
<td>not yet determined</td>
<td>dsDNA repair by NHEJ</td>
</tr>
<tr>
<td>Familial breast, ovarian cancer</td>
<td>BRCA1, BRCA2d</td>
<td>breast and ovarian carcinomas</td>
<td>homology-directed repair of dsDNA breaks</td>
</tr>
<tr>
<td>Werner</td>
<td>WRN</td>
<td>several cancers</td>
<td>exonuclease and DNA helicase g, replication</td>
</tr>
<tr>
<td>Bloom</td>
<td>BLM</td>
<td>solid tumors</td>
<td>DNA helicase, replication</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>(9 genes)f</td>
<td>AML, HNSCC</td>
<td>repair of DNA cross-links and ds breaks</td>
</tr>
<tr>
<td>Nijmegen breakg</td>
<td>NBS</td>
<td>mostly lymphomas</td>
<td>processing of dsDNA breaks, NHEJ</td>
</tr>
<tr>
<td>Li–Fraumeni</td>
<td>TP53</td>
<td>multiple cancers</td>
<td>DNA damage alarm protein</td>
</tr>
<tr>
<td>Li–Fraumeni</td>
<td>CHK2</td>
<td>colon, breast</td>
<td>kinase signaling DNA damage</td>
</tr>
</tbody>
</table>

*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.

bXeroderma 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.

cAtaxia telangiectasia, small number of cases.

dMutant germ-line alleles of BRCA1 and BRCA2 together may account for 10–20% of identifiable human familial breast cancers.

eAn exonuclease digests DNA or RNA from one end inward; a DNA helicase unwinds double-stranded DNA molecules.

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

gThe 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.

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
Perspectives


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

Figure 9.1 Laboratory workflow for whole-genome sequencing.

Figure 9.2 Variant analysis and filtration in whole-genome sequencing.
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 occurs 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.
Copy-number variation in sporadic amyotrophic lateral sclerosis: a genome-wide screen
BRCA example
845G → A mutation in HFE gene
Hemochromatosis

APOE
Alzheimer’s

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
RNA (Ribonucleic Acid) vs DNA

Ribose sugar (vs deoxyribose)

Uracil instead of Thymine

Figure © 2000 by Griffiths et al.; All text material © 2008 by Steven M. Carr
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
• Once transcription starts several PolIII 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

Non-genomic actions

Genomic actions

Ligand dependent
- Gene activation
- Gene depression
- Gene repression
- Gene transrepression

Ligand independent
- Gene repression
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 EQUILIBRIUM 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)
RNA SPlicing

alpha-tropomyosin

Figure 1-17b The Biology of Cancer (© Garland Science 2007)
ALTERNATIVE SPLICING IN PCa

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

<table>
<thead>
<tr>
<th>2nd base</th>
<th>U</th>
<th>C</th>
<th>A</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>U</strong></td>
<td>UUU (Phe/F) Phenylalanine</td>
<td>UCU (Ser/S) Serine</td>
<td>UAU (Tyr/Y) Tyrosine</td>
<td>UGU (Cys/C) Cysteine</td>
</tr>
<tr>
<td></td>
<td>UUC (Phe/F) Phenylalanine</td>
<td>UCC (Ser/S) Serine</td>
<td>UAC (Tyr/Y) Tyrosine</td>
<td>UGC (Cys/C) Cysteine</td>
</tr>
<tr>
<td></td>
<td>UUA (Leu/L) Leucine</td>
<td>UCA (Ser/S) Serine</td>
<td>UAA Ochre (Stop)</td>
<td>UGA Opal (Stop)</td>
</tr>
<tr>
<td></td>
<td>UUG (Leu/L) Leucine</td>
<td>UCG (Ser/S) Serine</td>
<td>UAG Amber (Stop)</td>
<td>UGG (Trp/W) Tryptophan</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>CUU (Leu/L) Leucine</td>
<td>CCU (Pro/P) Proline</td>
<td>CAU (His/H) Histidine</td>
<td>CGU (Arg/R) Arginine</td>
</tr>
<tr>
<td></td>
<td>CUC (Leu/L) Leucine</td>
<td>CCC (Pro/P) Proline</td>
<td>CAC (His/H) Histidine</td>
<td>CGC (Arg/R) Arginine</td>
</tr>
<tr>
<td></td>
<td>CUA (Leu/L) Leucine</td>
<td>CCA (Pro/P) Proline</td>
<td>CAA (Gln/Q) Glutamine</td>
<td>CGA (Arg/R) Arginine</td>
</tr>
<tr>
<td></td>
<td>CUG (Leu/L) Leucine</td>
<td>CGC (Pro/P) Proline</td>
<td>CAG (Gln/Q) Glutamine</td>
<td>CGG (Arg/R) Arginine</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>AUU (Ile/I) Isoleucine</td>
<td>ACU (Thr/T) Threonine</td>
<td>AAU (Asn/N) Asparagine</td>
<td>AGU (Ser/S) Serine</td>
</tr>
<tr>
<td></td>
<td>AUC (Ile/I) Isoleucine</td>
<td>ACC (Thr/T) Threonine</td>
<td>AAC (Asn/N) Asparagine</td>
<td>AGC (Ser/S) Serine</td>
</tr>
<tr>
<td></td>
<td>AUG (Met/M) Methionine</td>
<td>ACA (Thr/T) Threonine</td>
<td>AAA (Lys/K) Lysine</td>
<td>AGA (Arg/R) Arginine</td>
</tr>
<tr>
<td></td>
<td>GUA (Val/V) Valine</td>
<td>GCA (Ala/A) Alanine</td>
<td>GAA (Glu/E) Glutamic acid</td>
<td>GGA (Gly/G) Glycine</td>
</tr>
<tr>
<td></td>
<td>GUG (Val/V) Valine</td>
<td>GCC (Ala/A) Alanine</td>
<td>GAG (Glu/E) Glutamic acid</td>
<td>GGG (Gly/G) Glycine</td>
</tr>
</tbody>
</table>

Selection of notable mutations, ordered in a standard table of the genetic code of amino acids.

Clinically important missense mutations generally change the properties of the coded amino acid residue between being basic, acidic, polar or nonpolar, while nonsense mutations result in a stop codon.

Amino acids
- Basic
- Acidic
- Polar
- Nonpolar (hydrophobic)

Polyglutamine (PolyQ) Diseases
- Huntington's disease
- Spinocerebellar ataxia (SCA) (most types)
- Spinobulbar muscular atrophy (Kennedy disease)
- Dentatorubral-pallidolysian atrophy

Mutation type
- Trinucleotide repeat
- Deletion
- Missense
- Nonsense

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/ENCOD...
Co-association between transcription factors.

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
No meat at all? Are you sure you’re getting enough protein?
RIBOSOMES

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

Growing polypeptide chain

Peptidyl-transferase center

Decoding center

Movement of ribosome

Deacylated tRNA released from E site
DEGENERATE CODE

aa read from 3pbs
4bp x 4bp x 4bp = 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
Role of 5'- and 3'-untranslated regions of mRNAs in human diseases
Sangeeta Chatterjee and Jayanta K. Pal
Role of 5' and 3'-untranslated regions of mRNAs in human diseases

Sangeeta Chatterjee and Jayanta K. Pal


Role of 5' and 3'-untranslated regions of mRNAs in various diseases

Figure 2. Involvement of various regulatory elements of 5'- and 3'-UTRs of mRNAs in various diseases

5'-UTR
- Mutations affecting length and secondary structure
  - Breast cancer
- uORFs
  - Hereditary thrombocythemia
  - Alzheimer's disease
  - Bipolar affective disorder (BPAD)
  - Arrhythmogenic right ventricular cardiomyopathy/dysplasia (AVRC)
  - Melanoma
- IRES
  - X-linked Charcot-Marie-tooth disease (CMTX)
  - Multiple myeloma
  - Fragile X syndrome (FXS)
- Self complementary Stem-loop structures and RNA binding Proteins
  - Hereditary hyperferritinemia/cataract syndrome (HHCS)

3'-UTR
- Mutations Affecting
  - Termination Codon
    - Epidermolysis bullosa simplex (EBS)
    - Aniridia
  - Polyadenylation Signal
    - Hemoglobin H (HbH) disease
    - Immune dysfunction, polyendocrinopathy, enteropathy, X-linked (IPEX)
  - Secondary Structure
    - Congenital heart disease (CHD)
    - Arrhythmogenic right ventricular cardiomyopathy/dysplasia (AVRC)
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 downstream 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.
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...?!