Genetic Code

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The Genetic Code

- Building Blocks of DNA
  - Phosphoric acid, deoxyribose: form the helical strands
  - 4 nitrogenous bases
    - Two purines: adenine and guanine
    - Two Pyrimidines: thymine and cytosine
- Nucleotides:
  - Formed by combining one molecule of phosphoric acid, deoxyribose and one of the 4 bases
    - Deoxyadenylic acid
    - Deoxythymidylic acid
    - Deoxyguanylic acid
    - Deoxycytidylic acid

Nucleotides

- Nucleotides are molecules that, when joined together, make up the structural units of RNA and DNA.
- In addition, nucleotides play central roles in metabolism. In that capacity, they:
  - Serve as sources of chemical energy (adenosine triphosphate and guanosine triphosphate),
  - Participate in cellular signaling (cyclic guanosine monophosphate and cyclic adenosine monophosphate)
  - Are incorporated into important cofactors of enzymatic reactions (coenzyme A, flavin adenine dinucleotide, flavin mononucleotide and nicotinamide adenine dinucleotide phosphate).

Nucleotides

- A nucleotide is composed of a nucleobase (nitrogenous base), a five-carbon sugar (either ribose or 2'-deoxyribose), and one to three phosphate groups. Together, the nucleobase and sugar comprise a nucleoside.
  - The phosphate groups form bonds with either the 2, 3, or 5-carbon of the sugar, with the 5-carbon site most common. Cyclic nucleotides form when the phosphate group is bound to two of the sugar's hydroxyl groups.
- Ribonucleotides are nucleotides where the sugar is ribose and deoxyribonucleotides contain the sugar deoxyribose. Nucleotides can contain either a purine or pyrimidine base.
- Nuclei acids are polymeric macromolecules made from nucleotide monomers. In DNA, the purine bases are adenine and guanine, while the pyrimidines are thymine and cytosine. RNA uses uracil in place of thymine.

The Genetic Code

- The purine base adenine of one strand always bonds with the pyrimidine base thymine. Guanine always bonds with cytosine.
- The base pairs are thus CG, GC, AT or TA
- The genetic code consists of successive triplets or code words. These triplets eventually control the sequence of amino acids deposited in a protein molecule

The Genetic Code

- Transcription
  - Transferring the genetic code from DNA to RNA in the nucleus
    - The 2 DNA strands separate and one becomes a template for RNA synthesis. The code triplets in DNA cause the formation of complimentary code triplets, called Codons in the RNA.
- RNA
  - Contains ribose instead of deoxyribose
  - Thymine is replaced by another pyrimidine, uracil in the RNA nucleotides
- Activation of RNA Nucleotides: by RNA polymerase
  - 2 phosphate radicals are added to form triphosphates

The Genetic Code

- DNA strands have sequences of nucleotides called promoters. The RNA polymerase has a complementary structure that recognizes the promoter and attaches to it: an essential step on initiating the formation of RNA

- The polymerase temporarily unwinds the DNA and as it moves along it adds at each new stage, a new activated RNA nucleotide to the end of the newly forming RNA chain

The Genetic Code

- When the RNA polymerase reaches the end of the DNA gene, it encounters a sequence of DNA nucleotides called the chain-terminating sequence. This causes the polymerase to break away from the DNA. The DNA rebinds with its complimentary strand

- Messenger RNA carries the genetic code to the cytoplasm

- Transfer RNA transports activated amino acids to the ribosomes

  - Translation is the process whereby a messenger RNA travels through the ribosome, forming a protein molecule.

- Ribosomal RNA, with other proteins form ribosomes where proteins are assembled

Transcription and Translation

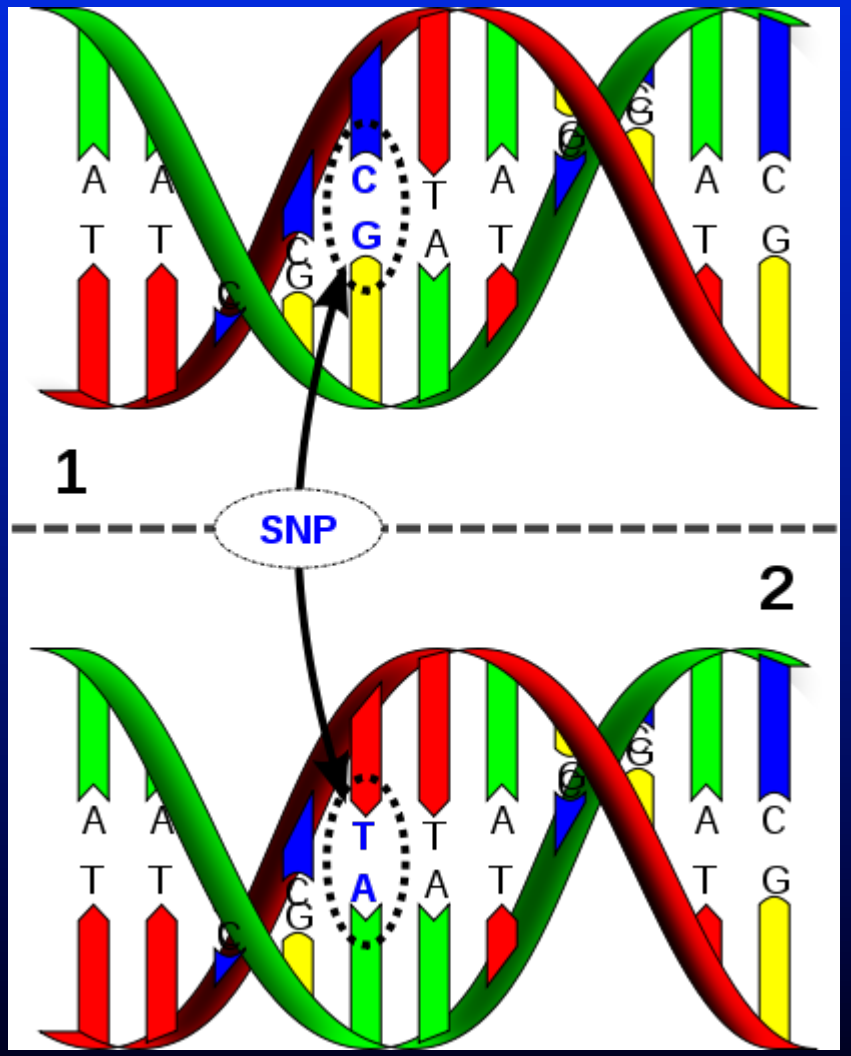
- **Transcription:** the process of constructing a messenger RNA molecule using a DNA molecule as a template with resulting transfer of genetic information to the messenger RNA
- **Translation:** the process of forming a protein molecule at a ribosomal site of protein synthesis from information contained in messenger RNA
- Messenger RNA (mRNA) is single-stranded. Its sequence of nucleotides is called "sense" because it results in a gene product (protein). Normally, its unpaired nucleotides are "read" by transfer RNA anticodons as the ribosome proceeds to **translate** the message.

Translation: Mutations

- **Missense**: relating to or being a genetic mutation involving alteration of one or more codons so that different amino acids are determined
- **Nonsense**: genetic information consisting of one or more codons that do not code for any amino acid and usually cause termination of the molecular chain in protein synthesis
- **Antisense**: having a sequence complementary to a segment of genetic material; *specifically* **:** of, being, relating to, or possessing a sequence of DNA or RNA that is complementary to and pairs with a specific messenger RNA blocking it from being translated into protein and serving to inhibit gene function

Single Nucleotide Polymorphisms

- A single-nucleotide polymorphism (SNP, pronounced snip) is a DNA sequence variation occurring when a single nucleotide — A (adenine), T (thymine), C (cytosine),or G (guanine) — in the genome (or other shared sequence) differs between members of a species (or between paired chromosomes in an individual).
- For example, two sequenced DNA fragments from different individuals, AAGCCTA to AAGCTTA, contain a difference in a single nucleotide. In this case we say that there are two alleles: C and T.
- Almost all common SNPs have only two alleles.



Yue, P; Moult, J (Mar 2006). "Identification and analysis of deleterious human SNPs". Journal of molecular biology 356 (5): 1263–74.

Single Nucleotide Polymorphisms

- For a variation to be considered a SNP, it must occur in at least 1% of the population. SNPs, which make up about 90% of all human genetic variation, occur every 100 to 300 bases along the 3-billion-base human genome.
- Two of every three SNPs involve the replacement of cytosine (C) with thymine (T).
- SNPs do not cause disease, but they can help determine the likelihood that someone will develop a particular illness. One of the genes associated with Alzheimer's disease, apolipoprotein E or ApoE, is a good example of how SNPs affect disease development. ApoE contains two SNPs that result in three possible alleles for this gene: E2, E3, and E4. Each allele differs by one DNA base, and the protein product of each gene differs by one amino acid.

http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml#snps

Single Nucleotide Polymorphisms

- Single nucleotide polymorphisms may fall within coding sequences of genes, non-coding regions of genes or in the intergenic regions between genes.
- SNPs within a coding sequence will not necessarily change the amino acid sequence of the protein that is produced, due to degeneracy of the genetic code.
- A SNP in which both forms lead to the same polypeptide sequence is termed **synonymous** (sometimes called a silent mutation) — if a different polypeptide sequence is produced they are **nonsynonymous**.
- A nonsynonymous change may either be missense or nonsense, where a missense change results in a different amino acid, while a nonsense change results in a stop codon.
- SNPs that are not in protein-coding regions may still have consequences for gene splicing, transcription factor binding, or the sequence of non-coding RNA.

Yue, P; Moult, J (Mar 2006). "Identification and analysis of deleterious human SNPs". Journal of molecular biology 356 (5): 1263–74.

Single Nucleotide Polymorphisms

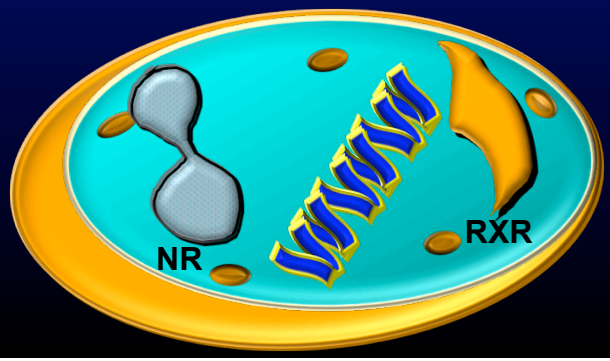
- Most SNPs are not responsible for a disease state. Instead, they serve as biological markers for pinpointing a disease on the human genome map, because they are usually located near a gene found to be associated with a certain disease. Occasionally, a SNP may actually cause a disease and, therefore, can be used to search for and isolate the disease-causing gene.
- The nomenclature for SNPs can be confusing: several variations can exist for an individual SNP and consensus has not yet been achieved.
- One approach is to write SNPs with a prefix, period and greater than sign showing the wild-type and altered nucleotide or amino acid; for example, c.76A>T.

http://www.ncbi.nlm.nih.gov/About/primer/snps.html

Ogino, S; Gulley, ML; Den Dunnen, JT; Wilson, RB; Association For Molecular Patholpogy Training And Education, Committtee (2007). " Standard Mutation Nomenclature in Molecular Diagnostics". The Journal of Molecular Diagnostics 9 (1): 1–6.

Genetic Regulation of Lipids

- At least 4 nuclear receptors (NRs) are affected by sterols & fatty acids and may regulate cholesterol and triglyceride metabolism.
  - Liver X receptor (LXR)
  - Hepatocyte Nuclear Factor-4-alpha (HNF-4-α)
  - Farnesol X Receptor (FXR)
  - Peroxisome Proliferator-Activated Receptors (PPARs)
- These often heterodimerize with Retinoid X Receptor (RXR)



Chawla A et al. Science 2001:294:1866-1870