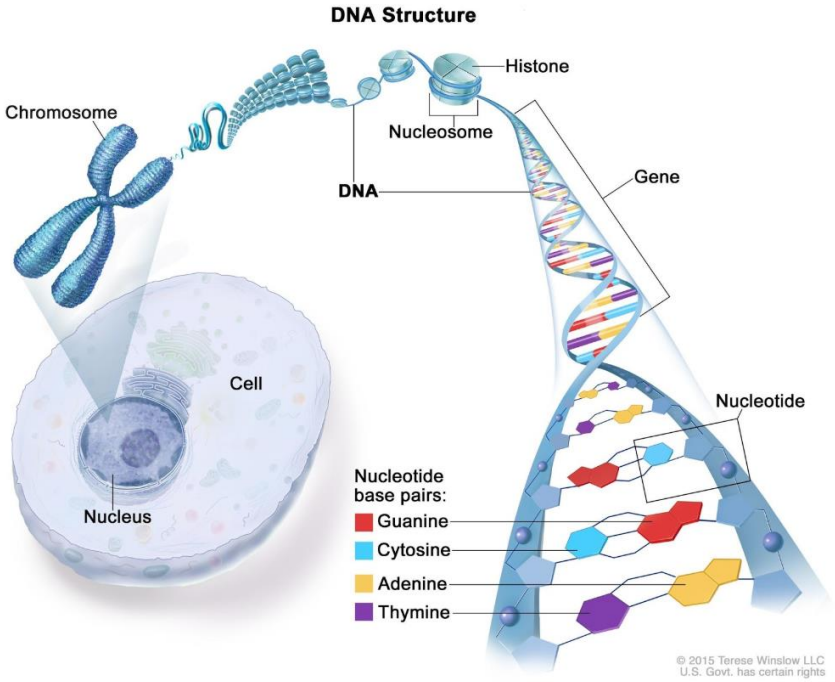
Molecular pathology

เรียบเรียงโดย พญ.ฑิชกร พานิช
อาจารย์ที่ปรึกษา อ.นพ.ปัญญา ทวีปวรเดช

Definition and Examples

- the study of molecules in a disease state. In this context, the molecules studied are DNA, RNA and/or protein.



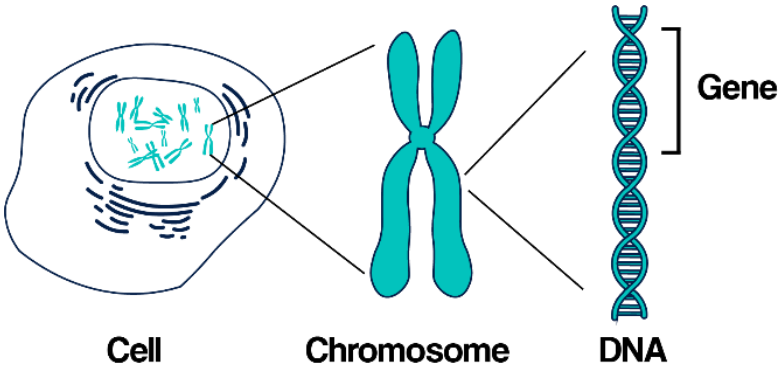
DNA MOLECULE 3 Component:

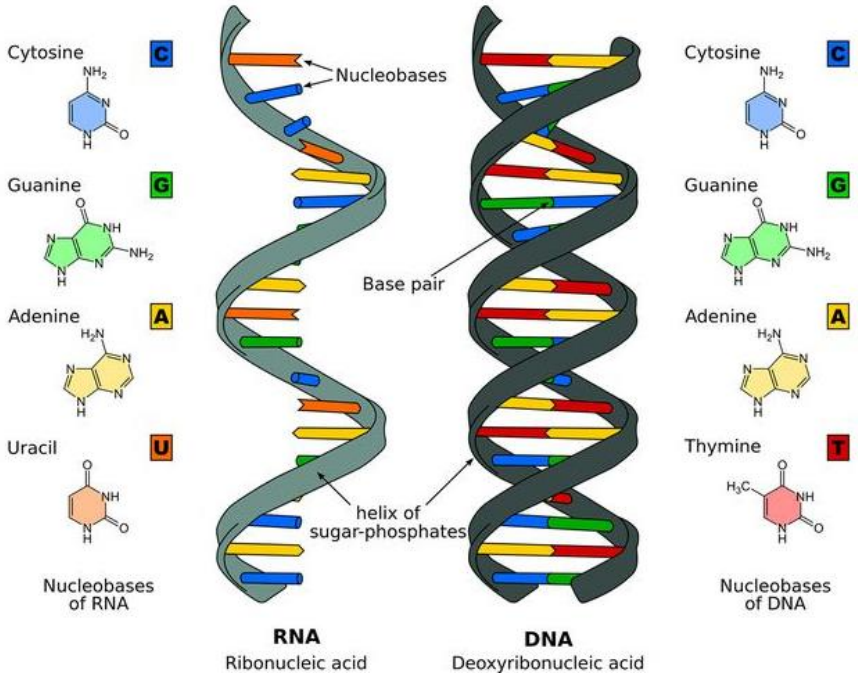
- Nitrogenous base A, G, C, T
- 5-Carbon sugar molecule
- Phosphate molecule

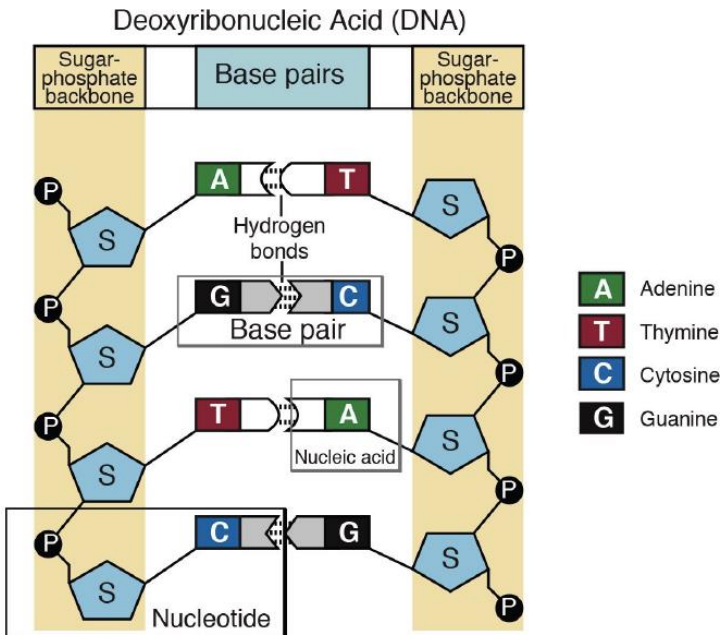
NUCLEOSIDE = Base + Pentose

NUCLEOTIDE = Nucleoside+ Phosphate

GENE = Consists of sequence of nucleotide at the given position on given chromosome code spacific protine or RNA molecule







Definition and Examples I

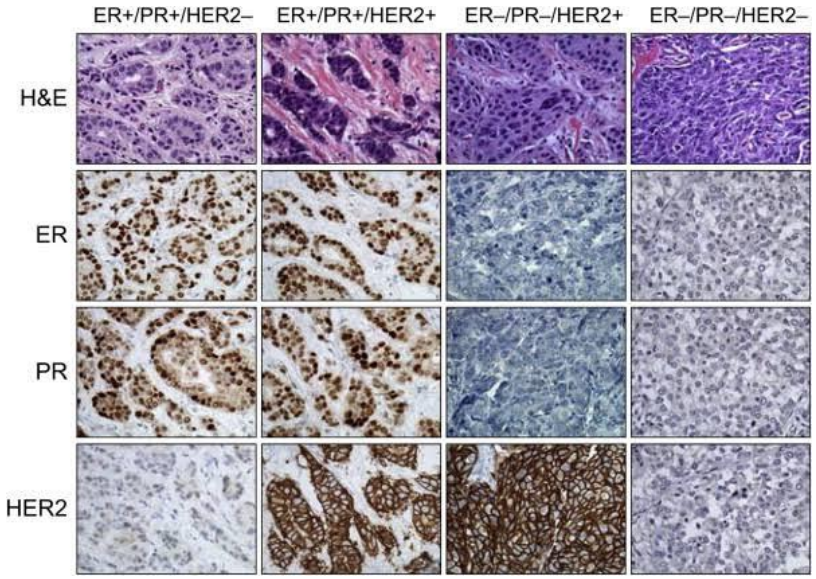
- Molecular pathology tests may look for the presence or absence of protein or RNA, or for an increase or decrease in the amount of these molecules
- Other molecular pathology tests look for rearrangements of large portions of DNA (chromosomal translocations) or for specific changes to the composition of genes (mutations).
- Molecular pathology can be used to diagnose disease and/or to guide the prevention and treatment of disease.
- In the field of cancer pathology, the demonstration of a specific gene mutation or rearrangement (fusion genes) can help confirm the diagnosis of certain lymphomas and sarcomas.

Definition and Examples II

- Molecular pathology can help with the prevention and/or treatment of disease in several ways. As an example of this, colorectal cancer patients can be tested for the presence of inherited mutations in genes such as APC or MMR genes.
- Molecular tests can help monitor the response of certain diseases to treatment and can detect whether or not the disease has returned, e.g. BCR-ABL testing in leukemias.
- There has been great recent interest in using molecular testing to predict the response of certain solid cancers to specific drugs.
- This predictive testing forms the basis of 'personalized medicine' for such cancer patients, including HER2 testing in breast and gastric cancer; EGFR and ALK1 testing in lung cancer; BRAF testing in melanoma; and KRAS testing in colorectal cancer. This form of predictive testing is currently a particular growth area in molecular pathology.

3 steps for IHC use

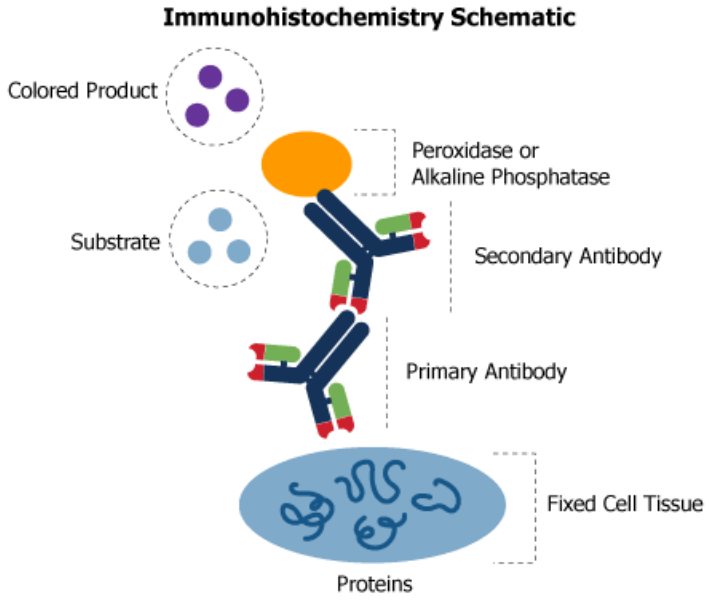
- Broad type of cancer carcinoma, melanoma, sarcoma, lymphoma
- Subtype of carcinoma
- Primary site of adenocarcinoma



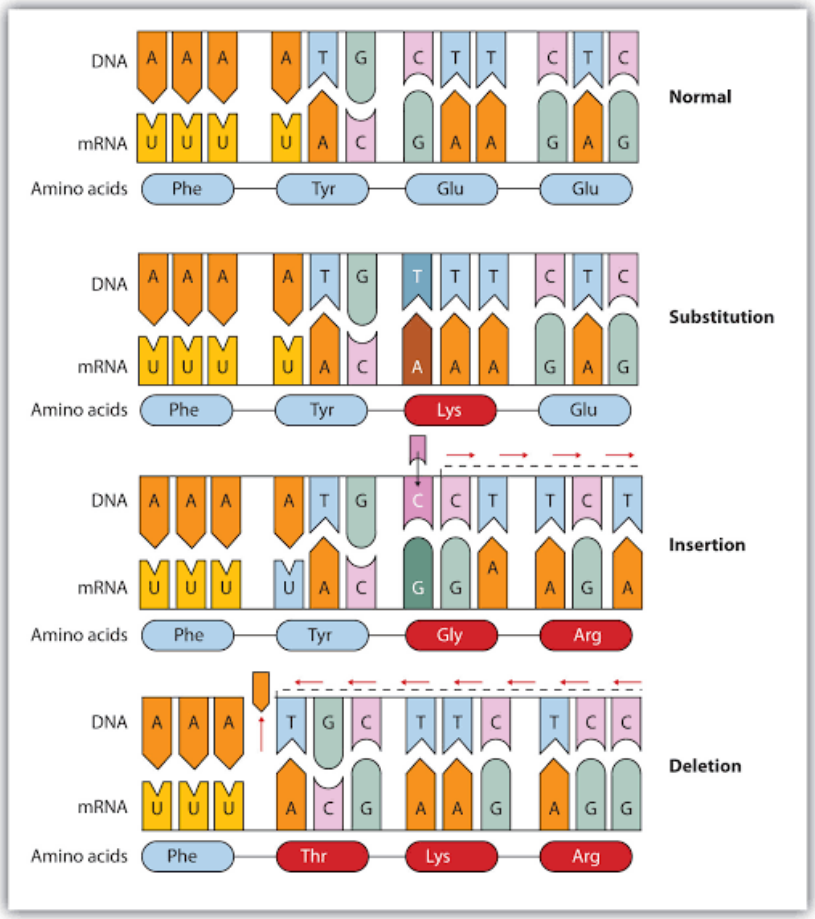
Genetic Alterations in Cancer

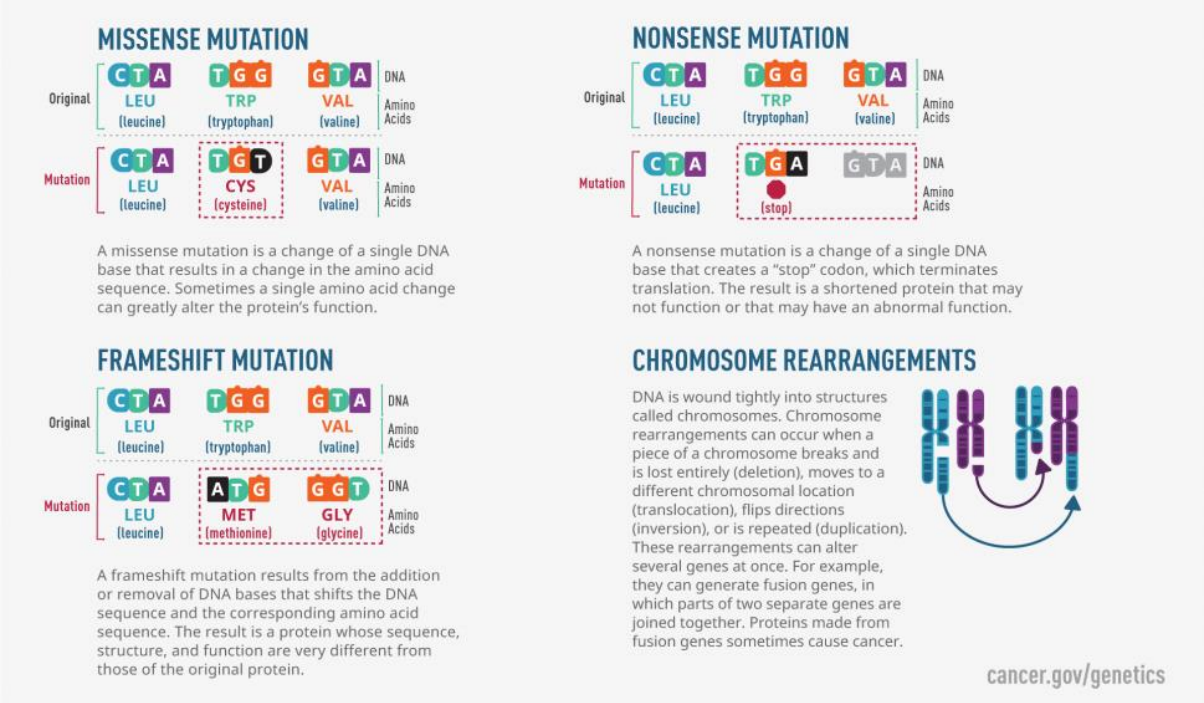
The four main types of genetic alterations in cancers

- Single nucleotide variants (SNVs), also known as point mutations. SNVs result from a base substitution at one nucleotide. These may result in a change in the amino acid sequence of the encoded protein (missense mutation) or a premature truncation of the protein (nonsense mutation).



- Small duplications of consecutive nucleotides, insertions or deletions involving one or a few nucleotides, or more complex mutations involving simultaneous deletions and insertions of one or a few bases (indels). These types of mutations may be "in-frame," resulting in the addition or subtraction of amino acids in the protein, or can cause a "frameshift," typically resulting in a premature truncation of the protein.





- Exon or gene copy number changes. Exon copy number changes include large duplications or deletions encompassing entire exons and affecting the functional domains of the protein. Gene copy number changes include amplifications or deletions of the entire gene.
- Structural variants (SVs) or large structural anomalies of genetic material including translocations or inversions that result from breakpoints between multiple chromosomes or within a single chromosome. These often result in fusion genes and associated fusion proteins.

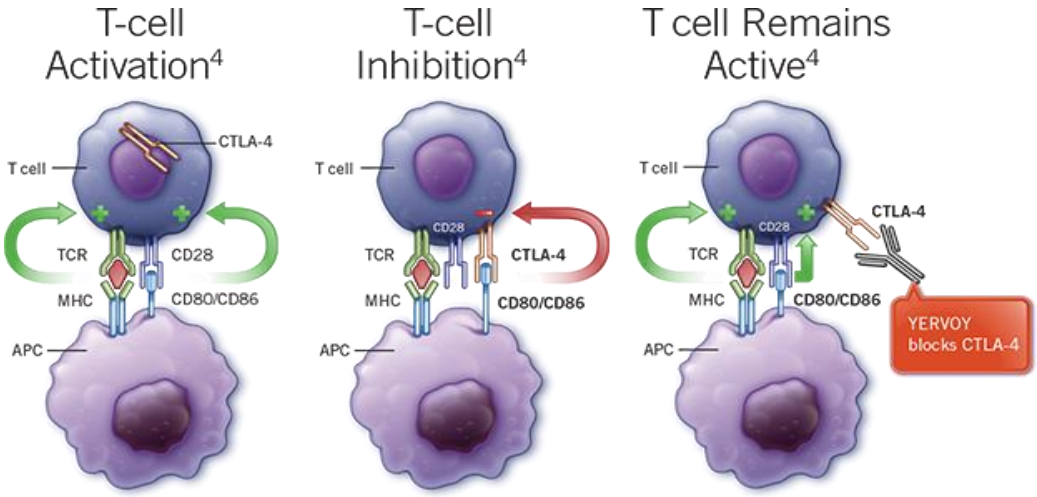
Molecular testing of oncology

- DNA
    - MUTATION ANALYSIS : SEQUENCING, SSCP
    - EPIGENETIC CHANGES : METHYLATION SENSITIVE ASSAY
    - COPY NUMBER ABERRATIONS : FISH , CGH
- RNA
    - GENE EXPRESSION PROFILING
    - RT-PCR
    - SAGE
- PROTEIN
    - IMMUNOHISTOCHEMISTRY
    - TISSUE MICROARRAYS
    - PROTEOMICS

Cancer Immunotherapy

Approaches to modulating the immune system:

- Vaccination with putative tumor antigens either as peptides or loaded within dendritic cells to enhance recognition;
- Adoptive immunotherapy where patients' own T cells are expanded ex vivo and reinfused;
- Reversing tumor cell-induced immune suppression. Blocking these
- Immunosuppressive mechanisms using blockade antibodies against T cell checkpoint molecules including CTLA-4 and the PD-1/PD-L1 axis in order to increase the function of endogenous antitumor T cells would help



Genomic medicine

- An emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision making) and the other implications of that clinical use.
- The field of cancer care is likely one of the first beneficiaries of Genomic Medicine. Cancer is a genetic disease. Genomic research is increasingly helping to inform and shape diagnosis and treatment recommendations.
- Tumors of the same group are molecular heterogeneous encompassing different lesions with distinct biological features.
- A key issue of the new treatment procedures is the fact that several so called targeted drugs may only be efficacious when tumors exhibit characteristic molecular features e.g. specific somatic mutation, gene amplification, chromosomal translocation.
- As classical histopathology is only partly able to mirror and predict clinical behavior of individual tumors, new molecular tests and methods will have to be added into the morphology-based diagnostic procedure to read a patient's tissue as 'deeply' as possible and to obtain combined information on morphological, genetic, proteomic as well as on epigenetic alterations.