cancer is fundamentally a genetic disease

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https://youtu.be/tA3xiwvz1HQ

https://youtu.be/aiA36xBFWdE

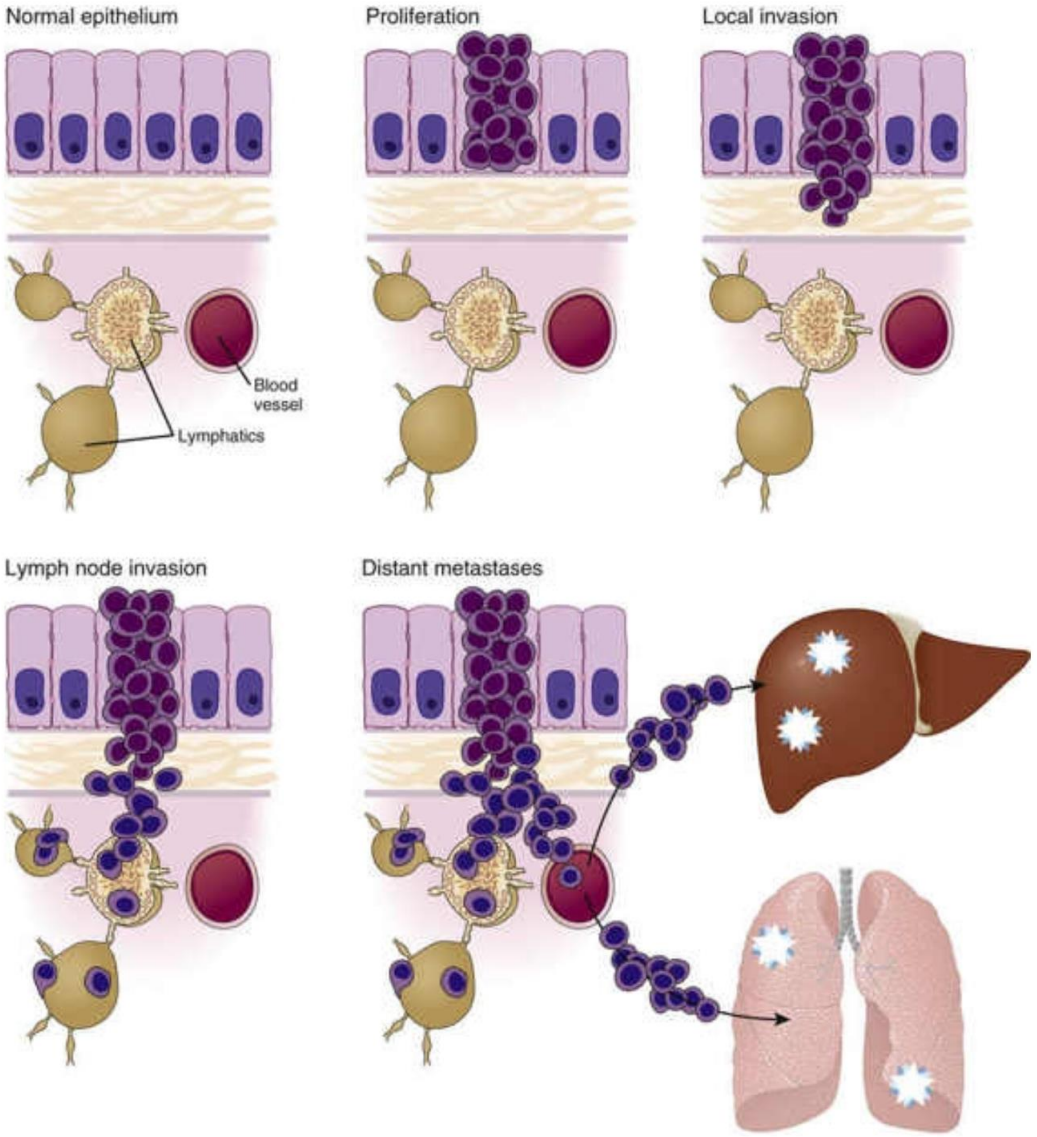
Neoplasia: is a disease process characterized by uncontrolled cellular proliferation leading to a mass or tumor (neoplasm).

Cancer is the name used to describe the more virulent forms of neoplasia

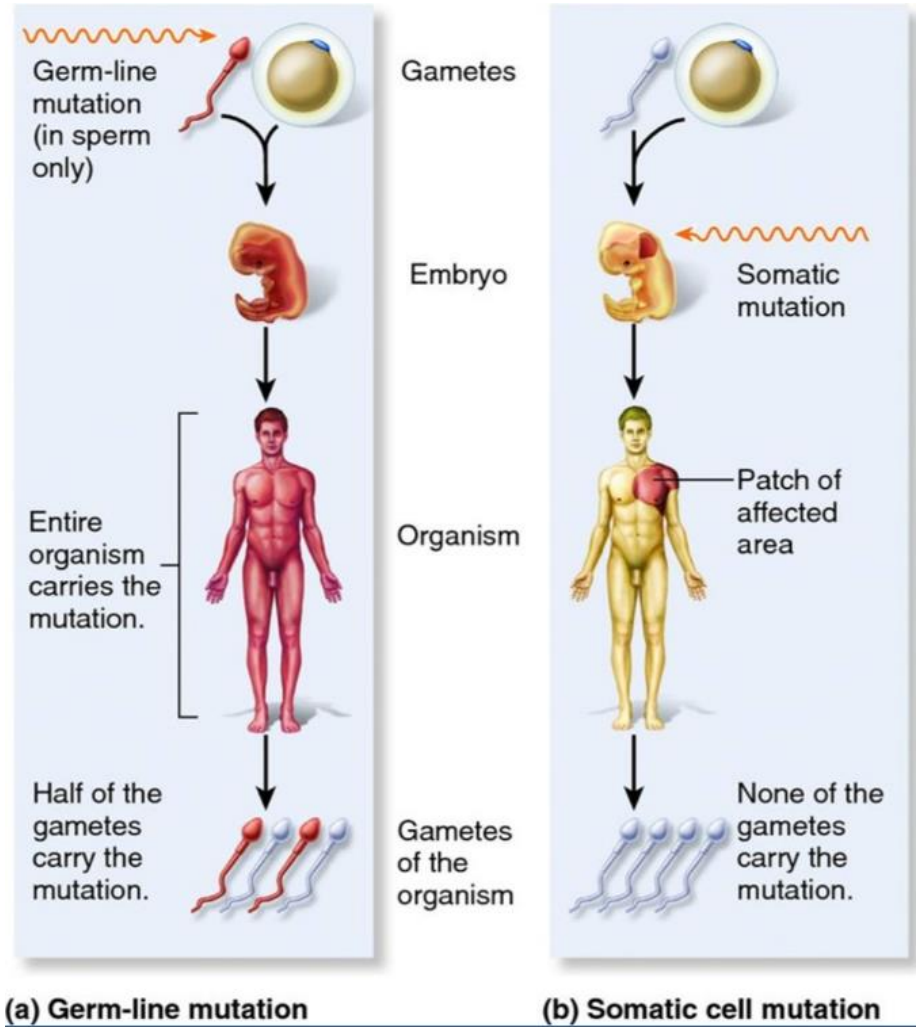
accumulation of cells in a neoplasm occurs because of an imbalance between the normal processes of cellular proliferation and cellular attrition.

For a neoplasm to be a cancer, however, it must also be malignant, which means that not only is its growth uncontrolled, it is also capable of invading neighboring tissues that surround the original site (the primary site) and can spread (metastasize) to more distant sites

Tumors that do not invade or metastasize are not cancerous but are referred to as benign tumors, although their abnormal function, size or location may make them anything but benign to the patient.



General scheme for development of a carcinoma in an epithelial tissue such as colonic epithelium. The diagram shows progression from normal epithelium to local proliferation, invasion across the lamina propria, spread to local lymph nodes, and final distant metastases to liver and lung.



Cancer is not a single disease but rather comes in many forms and degrees of malignancy.

There are three main classes of cancer:

- **Carcinomas**, which originate in epithelial tissue, such as the cells lining the intestine, bronchi, or mammary ducts. Most common

- **Sarcomas**, in which the tumor has arisen in mesenchymal tissue, such as bone, muscle, or connective tissue, or in nervous system tissue

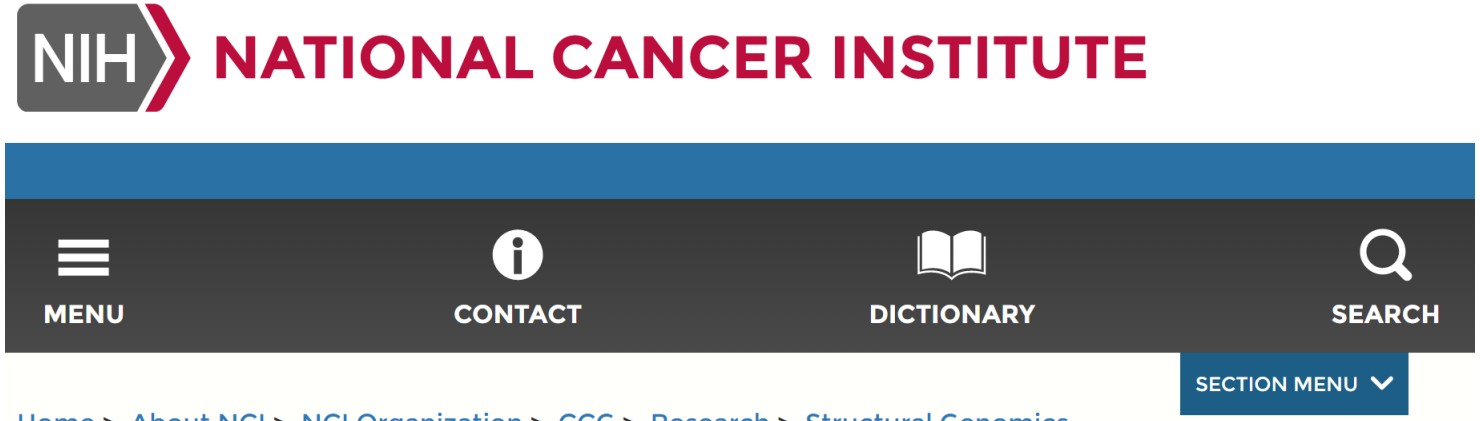
- **Hematopoietic** and **lymphoid** malignant neoplasms, such as leukemia and lymphoma, which spread throughout the bone marrow, lymphatic system, and peripheral blood.

Categories of Cancer

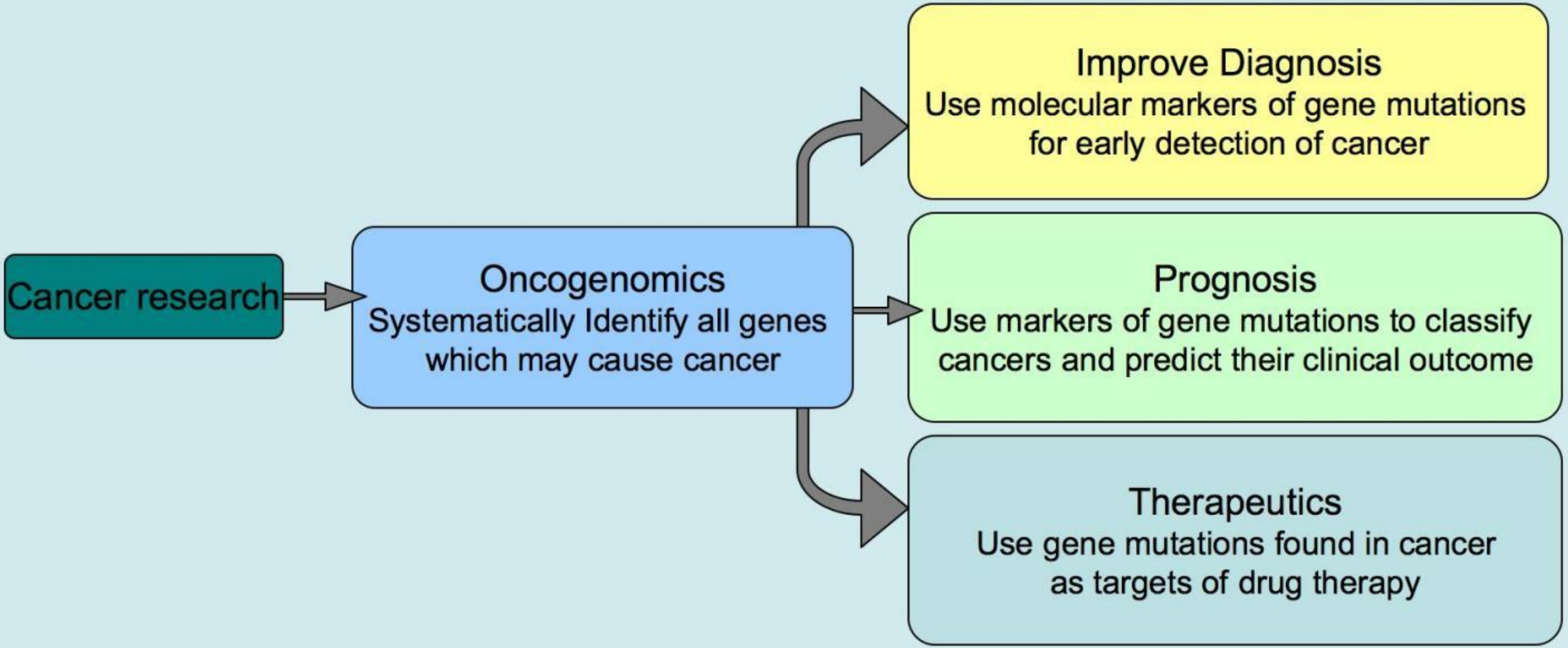
- Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs.
- Sarcoma: Cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
- Leukemia: Cancer that starts in blood-forming tissue such as the bone marrow & causes large numbers of abnormal blood cells to be produced & enter the blood.
- Lymphoma & myeloma: Cancers that begin in the cells of the immune system.

Within each of the major groups, tumors are classified by site, tissue type, histological appearance, degree of malignancy, chromosomal aneuploidy, and, increasingly, by which gene mutations and abnormalities in gene expression are found within the tumor.

Genomics—in particular the identification of mutations, altered epigenomic modifications, and abnormal gene expression in cancer cells—is vastly expanding our knowledge of why cancer develops and is
truly changing cancer diagnosis and treatment.



Overall goals of oncogenomics



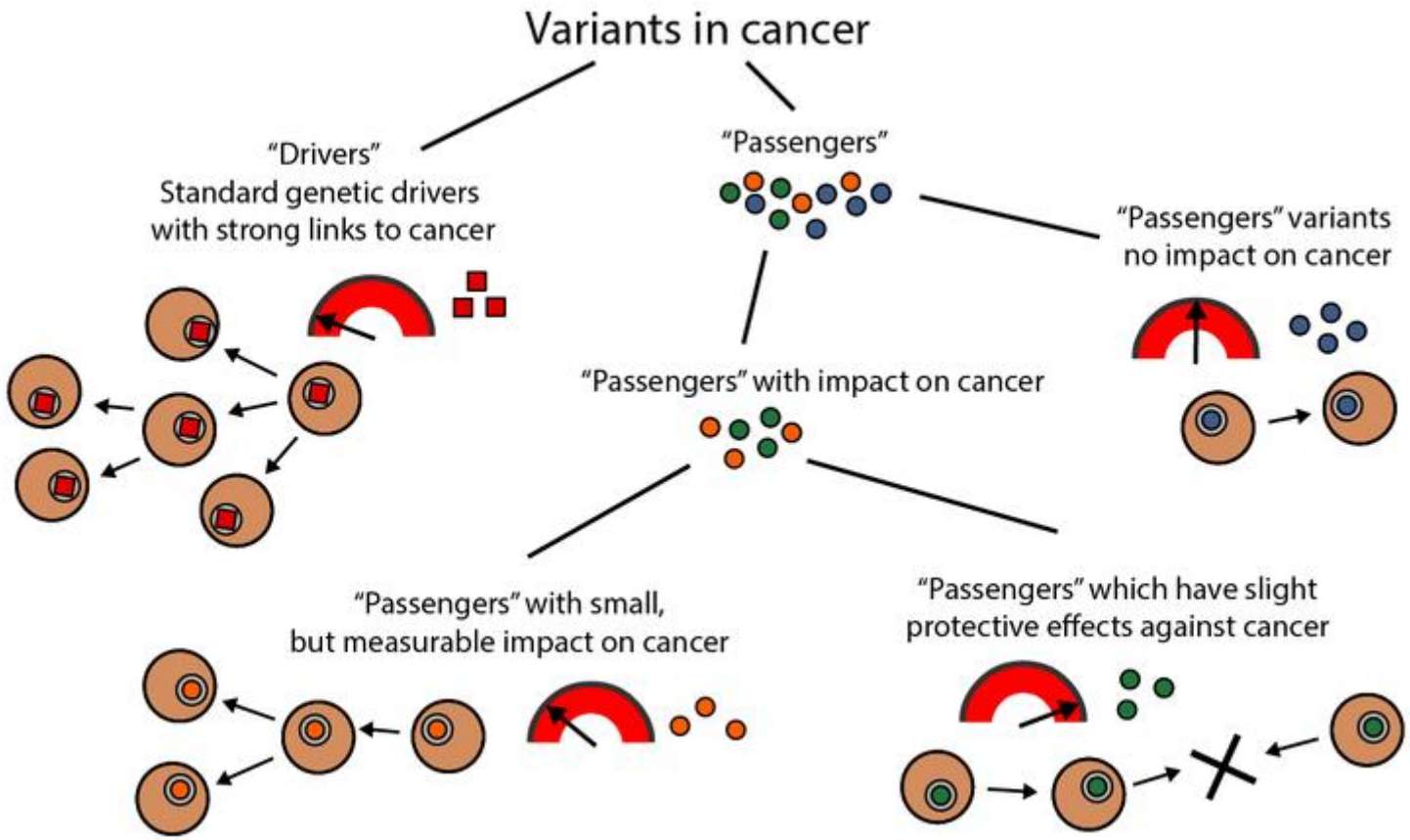
Driver and Passenger Gene Variants

The number of variants present in a tumor can vary from just a few to many tens of thousands.

Most mutations found through sequencing of tumor tissue appear to be random, are not recurrent in particular cancer types, and probably occurred as the cancer developed, rather than directly causing the neoplasia to develop or progress. Such mutations are referred to as "**passenger**" mutations

However, a subset of a few hundred genes has been repeatedly found to be mutated at high frequency in many samples of the same type of cancer or even in multiple different types of cancers, mutated in fact far too frequently to simply be passenger mutations.

These genes are thus presumed to be involved in the development or progression of the cancer itself and are therefore referred to as "**driver**" genes, that is, they harbor mutations (so-called driver gene mutations)

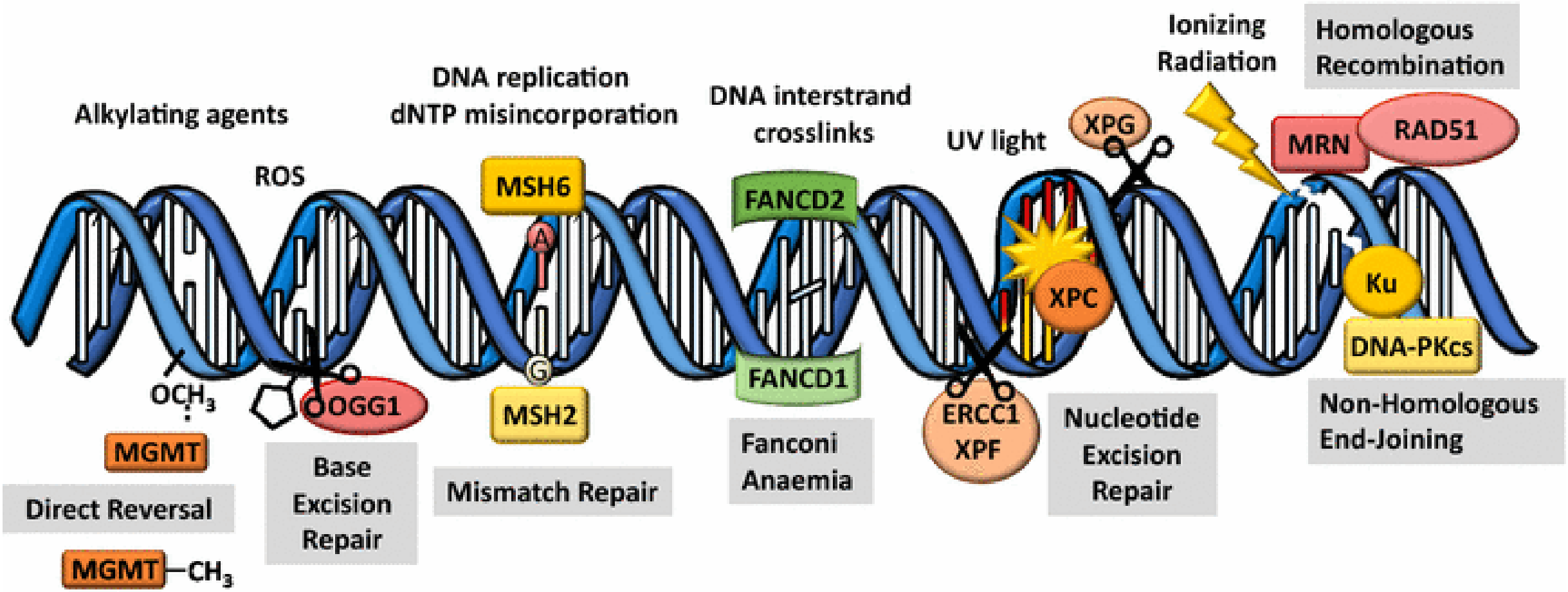


Although many driver genes are specific to particular tumor types, some, such as those in the **TP53** gene encoding the p53 protein, are found in the vast majority of cancers of many different types.

Although the most common driver genes are now known, it is likely that additional, less abundant driver genes will be identified as The Cancer Genome Atlas continues to grow.

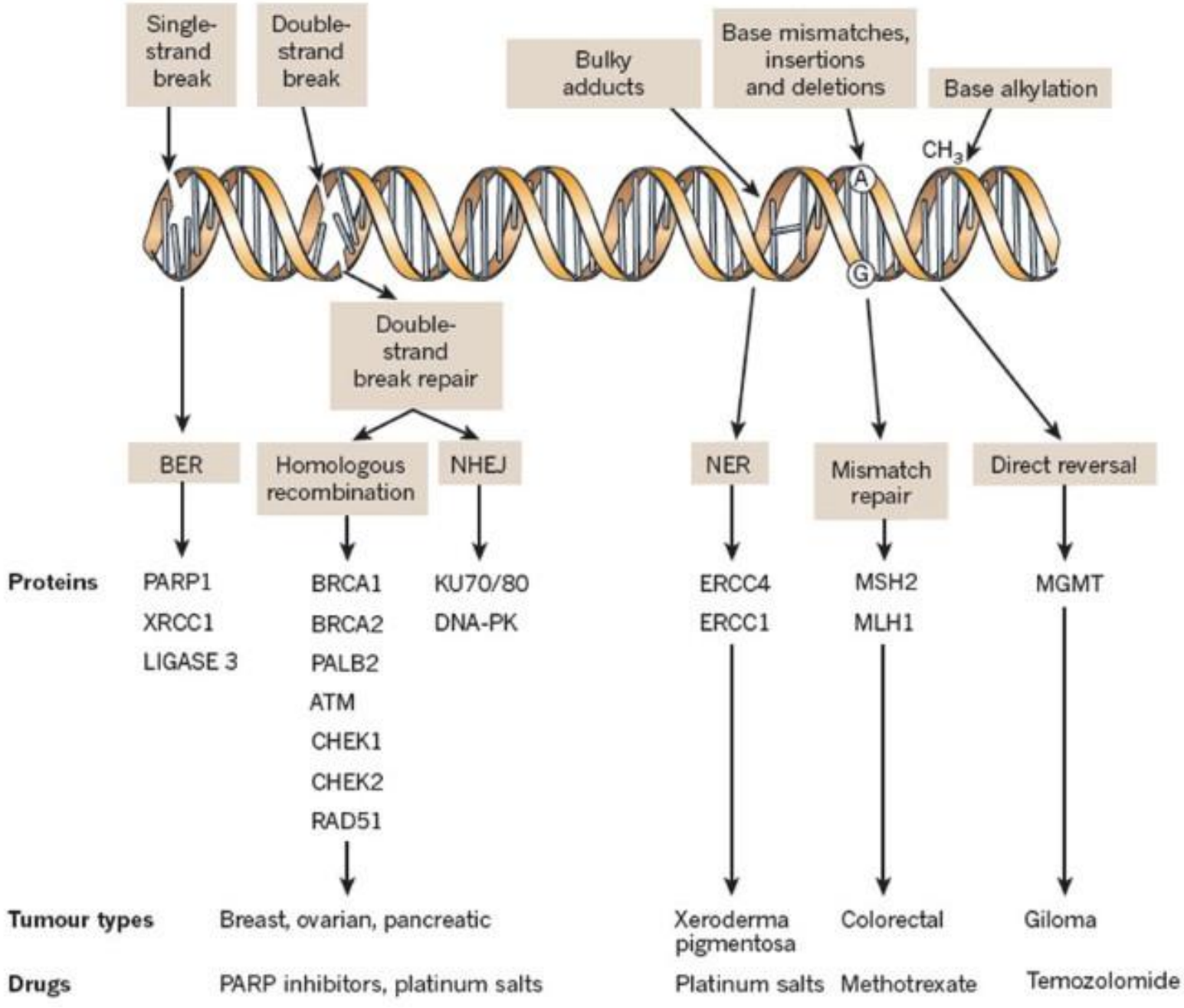
Spectrum of Driver Gene Mutations

Replication errors, environmental agents and failure of DNA repair could occur to **dividing and arrested** cells will increase the rate of variants around the genome

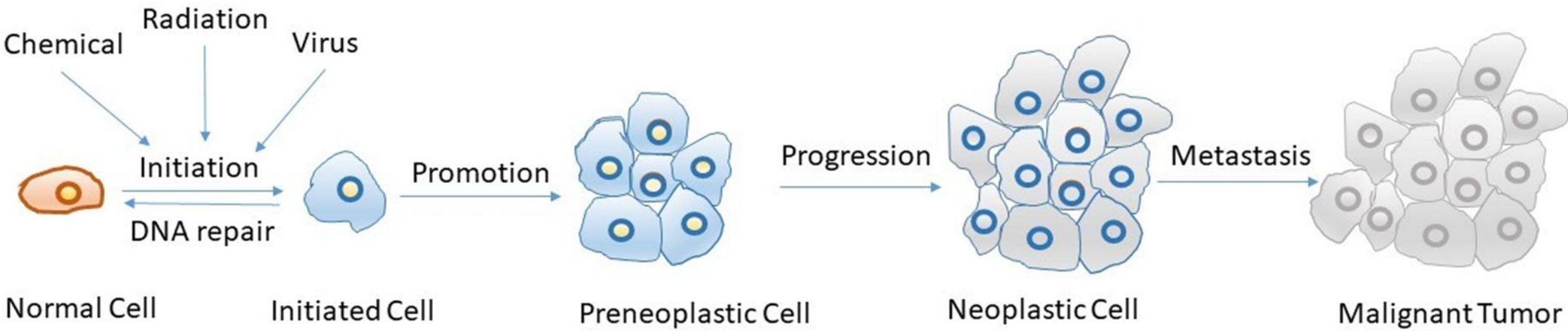


Spectrum of Driver Gene Mutations

If, by chance, mutations occur in critical driver genes in a particular cell, then the oncogenic process may be initiated.



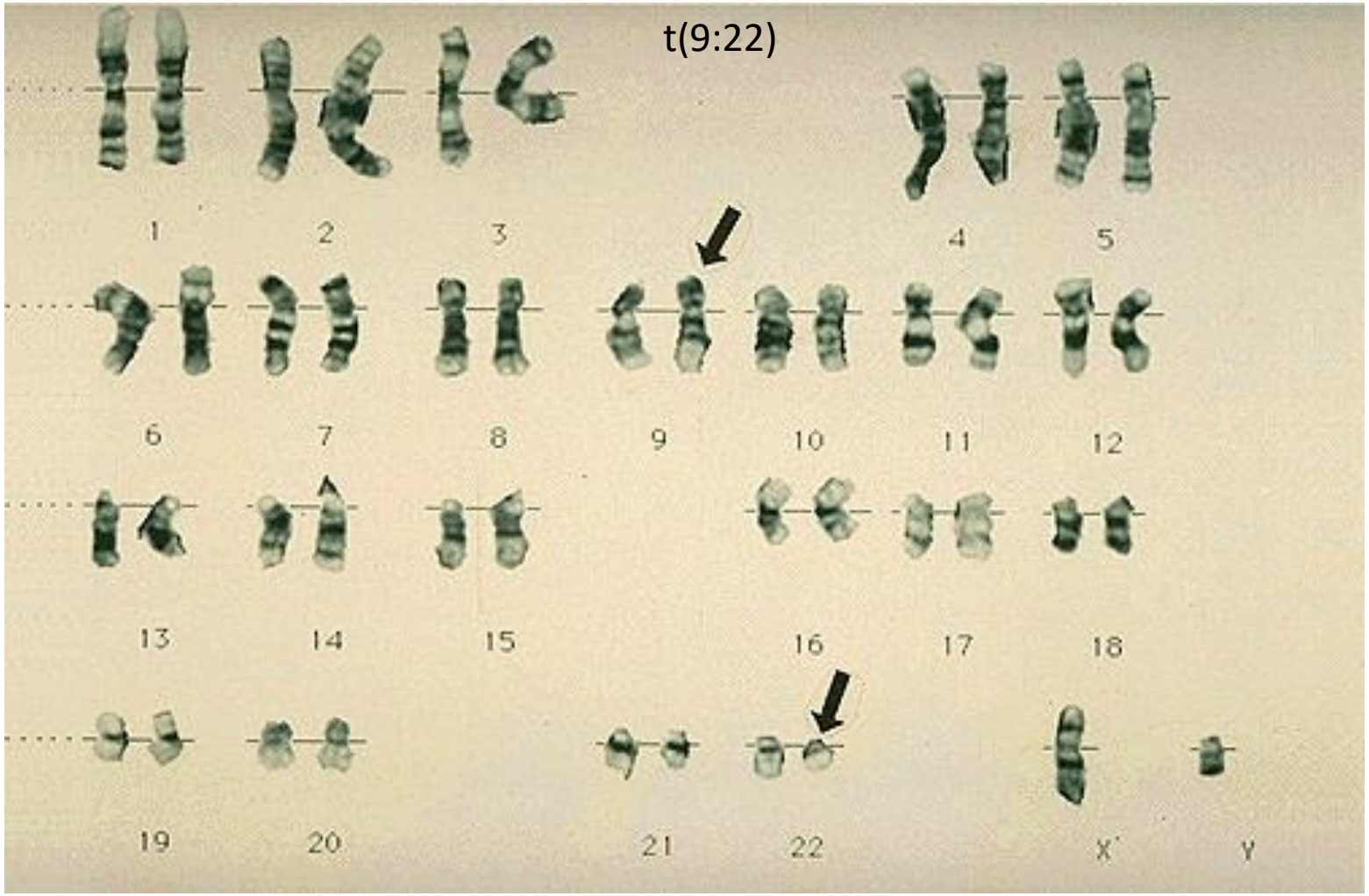
Multistep Carcinogenesis

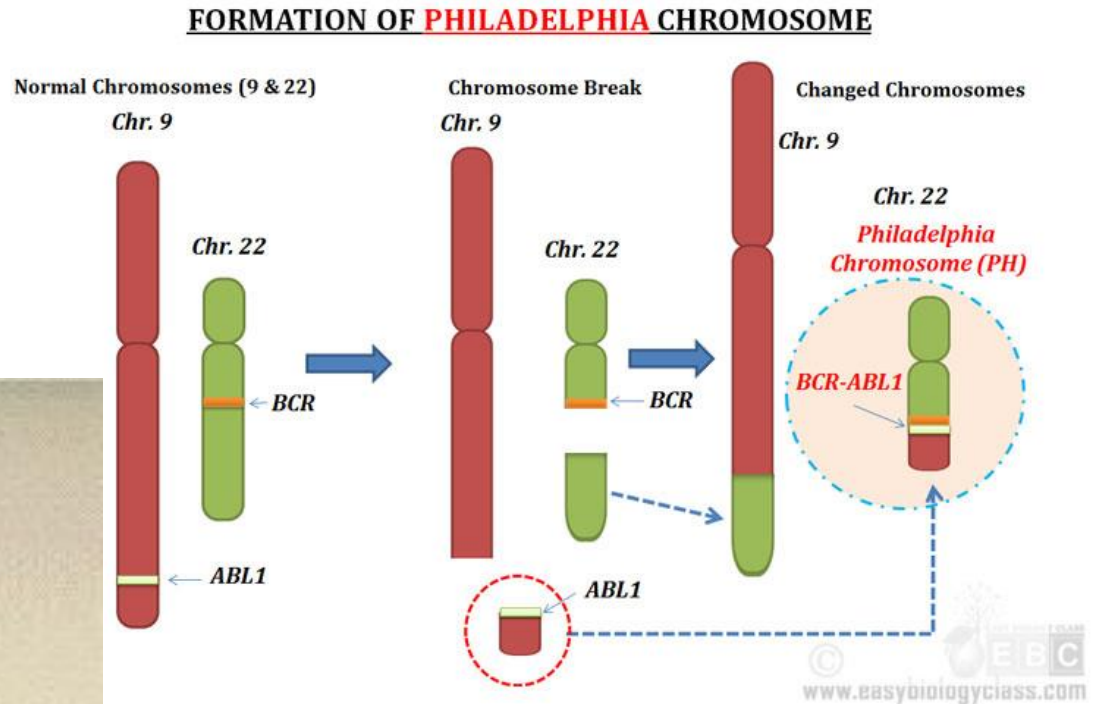


Driver mutations could occur on the chromosomal level

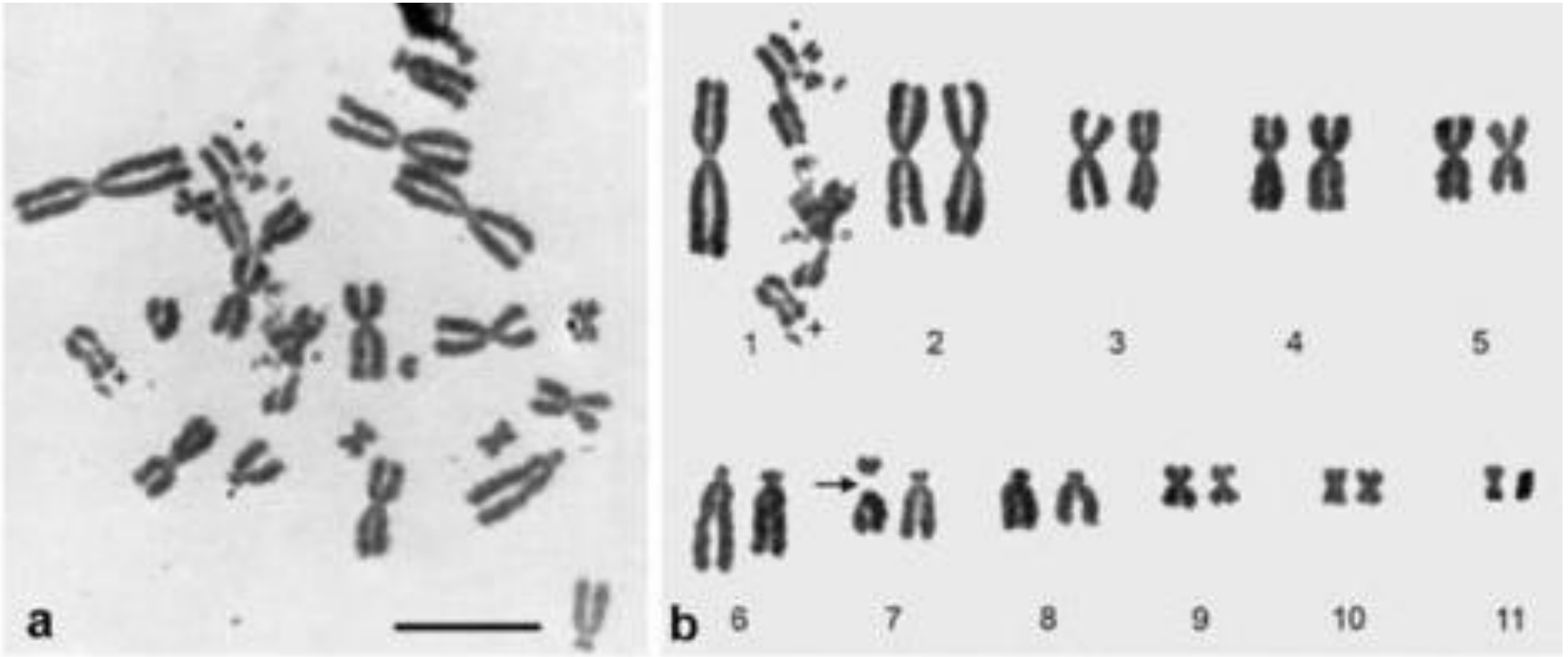
Chromosome and subchromosomal variants can also serve as driver mutations.

Particular translocations are sometimes highly specific for certain types of cancer a
involve specific genes
e.g., the BCR - ABL translocation in chronic myelogenous leukemia





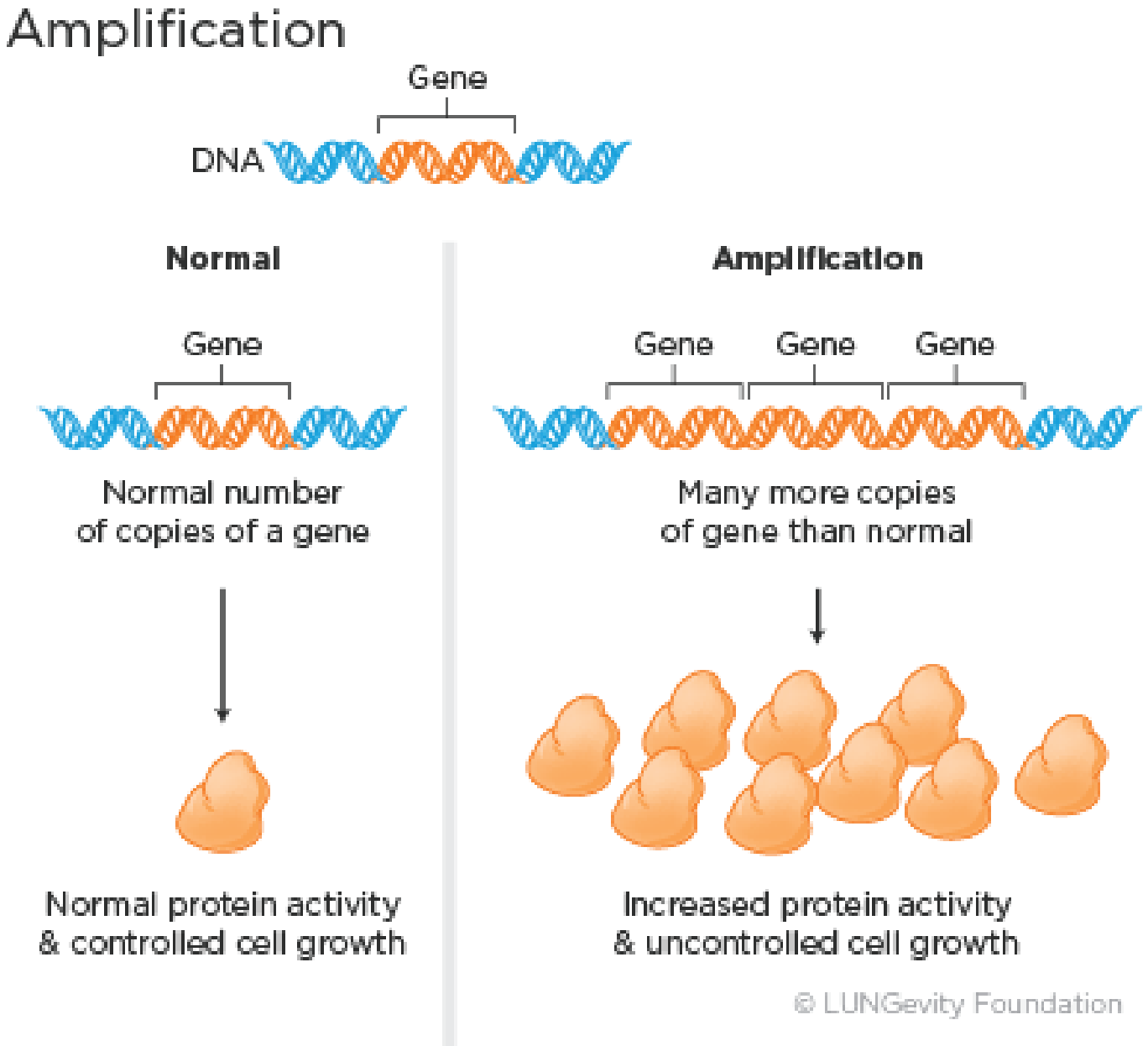
Other cancers can show **complex rearrangements** in which chromosomes break into numerous pieces and rejoin, forming novel and complex combinations (a process known as "**chromosome shattering** ").



Metaphase spreads with damaged chromosomes obtained after laser UV microirradiation of nuclei in living Chinese hamster cells. Nuclei in living Chinese hamster cells were microirradiated (k = 257 nm) at a single nuclear site comprising about 5% of the total nuclear area. Microirradiated cells were followed to the next mitosis (about 3-15 h) in medium with 1 mM caffeine.
a, b Metaphase spread (a) and the corresponding karyogram (b) from a diploid, fibroblastoid Chinese hamster cell reveal a shattered chromosome 1 and a break in a chromosome 7

large genomic alterations involving many kilobases of DNA can form the basis for **loss of function** or **increased function** of one or more driver genes.

Large genomic alterations include deletions of a segment of a chromosome or multiplication of a chromosomal segment to produce regions with many copies of the same gene (**gene amplification**).



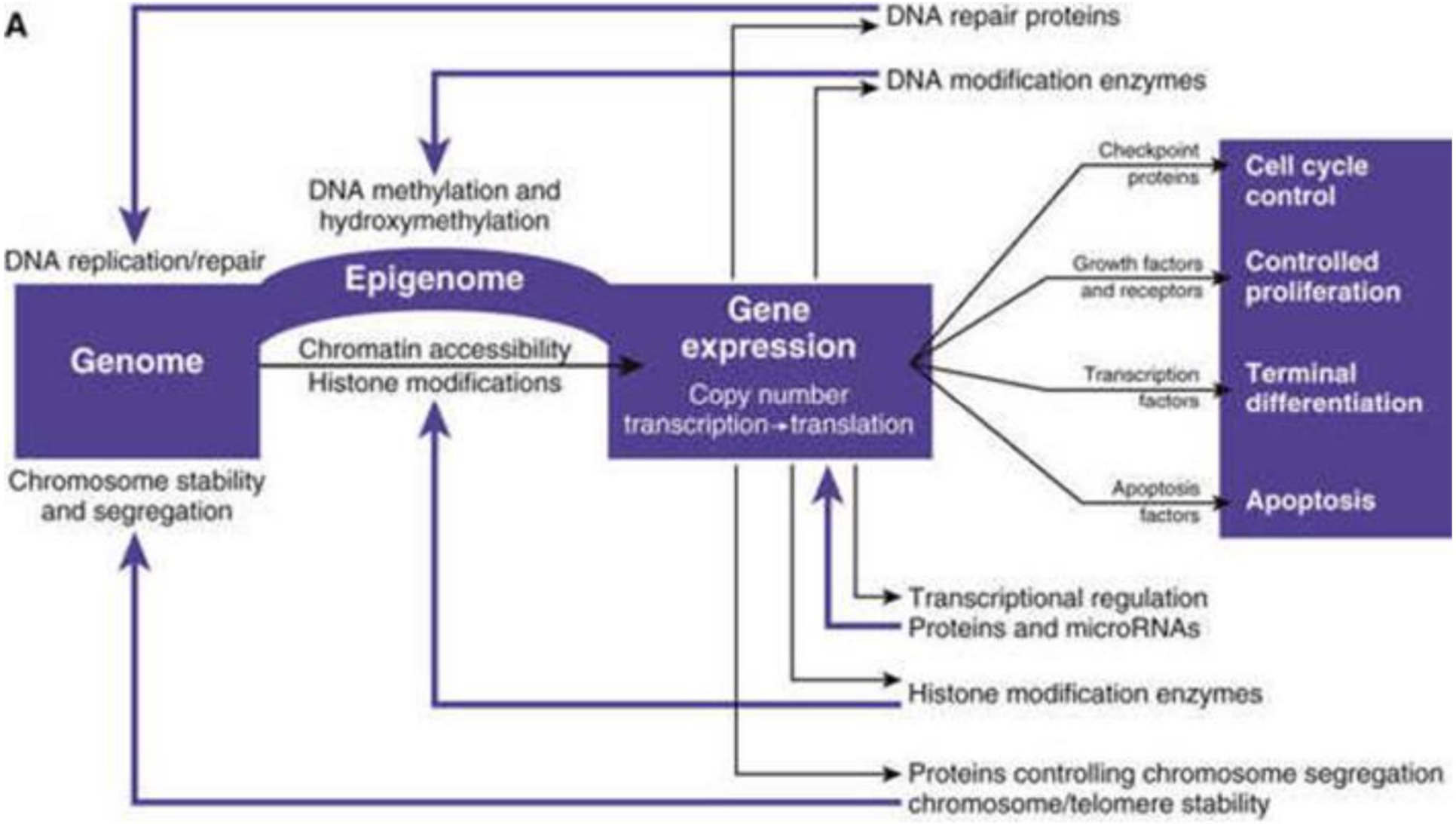
The Cellular Functions of Driver Genes

The nature of some driver gene mutations comes as no surprise: the mutations directly affect specific genes that regulate processes that are readily understood to be important in oncogenesis.

These processes include cell-cycle regulation, cellular proliferation, differentiation and exit from the cell cycle, growth inhibition by cell-cell contacts, and programmed cell death (apoptosis).

Classes of driver genes

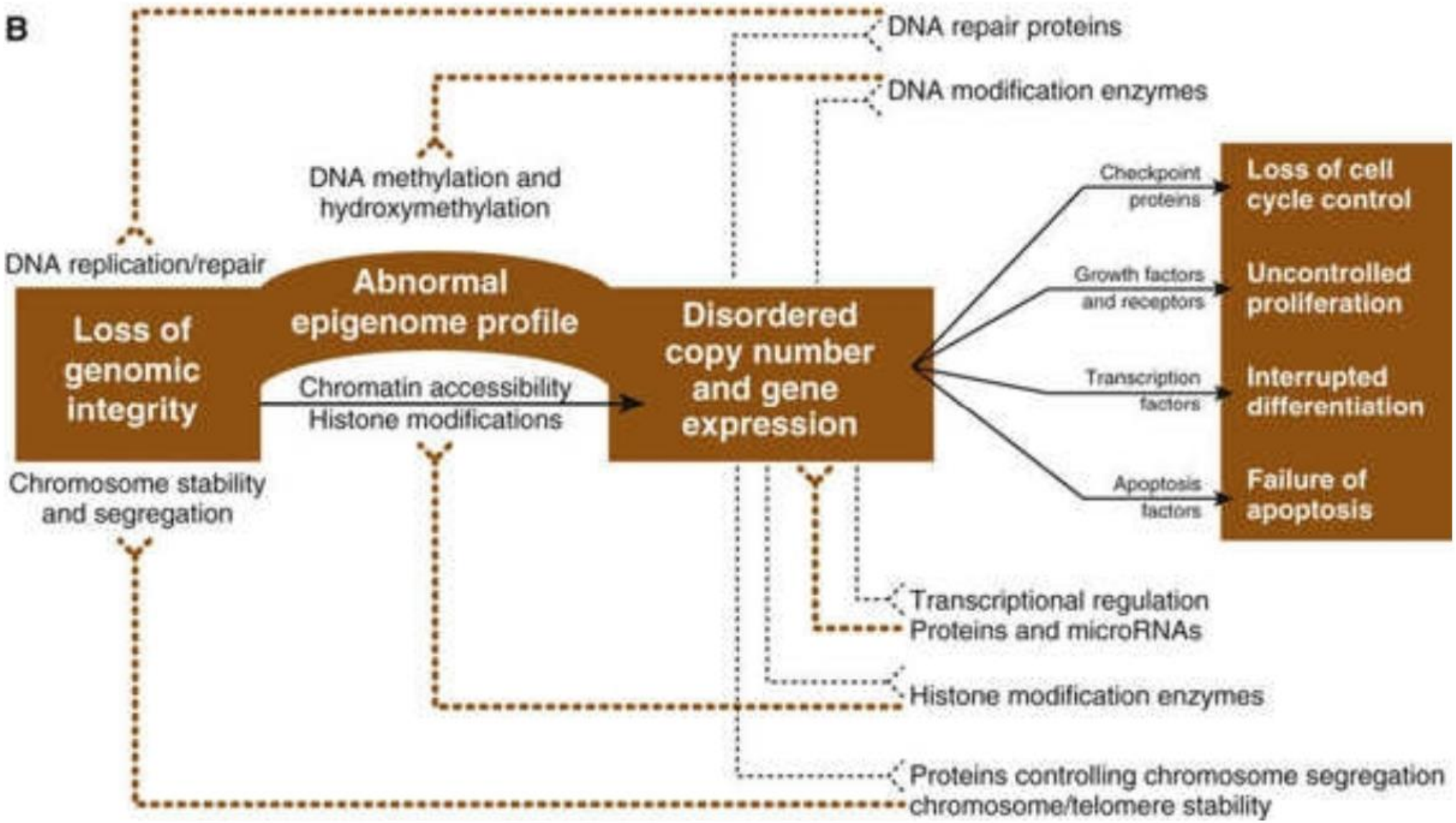
Genes with specific effects on cellular proliferation or survival	Genes with global effects on genome or DNA integrity
Cell-cycle regulation Cell-cycle checkpoint proteins Cellular proliferation signaling • Transcription factors • Receptor and membrane-bound tyrosine kinases • Growth factors • Intracellular serine-threonine kinases • PI3 kinases • G proteins and G protein–coupled receptors • mTOR signaling • Wnt/β-catenin signaling • Transcription factors Differentiation and lineage survival • Transcription factors protecting specific cell lineages • Genes involved in exit from cell cycle into G_0 Apoptosis	Genome integrity • Chromosome segregation • Genome and gene mutation • DNA repair • Telomere stability Gene expression: abnormal metabolites affecting activity of multiple genes/gene products Gene expression: epigenetic modifications of DNA/chromatin • DNA methylation and hydroxymethylation • Chromatin histone methylation, demethylation, and acetylation • Nucleosome remodeling • Chromatin accessibility and compaction (SWI/SNF complexes) Gene expression: post-transcriptional alterations • Aberrant mRNA splicing • MicroRNAs affecting mRNA stability and translation Gene expression: protein stability/turnover



Overview of normal genetic pathways controlling normal tissue homeostasis.

The information encoded in the genome (black arrows) results in normal gene expression, as modulated by the epigenomic state.

Many genes provide negative feedback (purple arrows) to ensure normal homeostasis.



Perturbations in neoplasia.
Abnormalities in gene expression (dotted black arrows) lead to a vicious cycle of positive feedback (brown dotted lines) of progressively more disordered gene expression and genome integrity.

Activated Oncogenes and Tumor Suppressor Genes

Both classes of driver genes—those with specific effects on cellular proliferation or survival and those with global effects on genome or DNA integrity —can be further **subdivided** into one of two functional categories depending on how, if mutated, they drive oncogenesis.

The first category includes **proto-oncogenes**
These are normal genes that, that promotes growth and survival of cells.

when mutated in very particular ways, become driver genes through alterations that lead to ***excessive levels of activity***

Once mutated in this way, driver genes of this type are referred to as **activated oncogenes** .

Only a **single mutation at one allele** can be sufficient for activation

The mutations that activate a proto-oncogene can **range** from highly specific point mutations causing dysregulation or hyperactivity of a protein, to chromosome translocations that drive overexpression of a gene, to gene amplification events that create an overabundance of the encoded mRNA and protein product

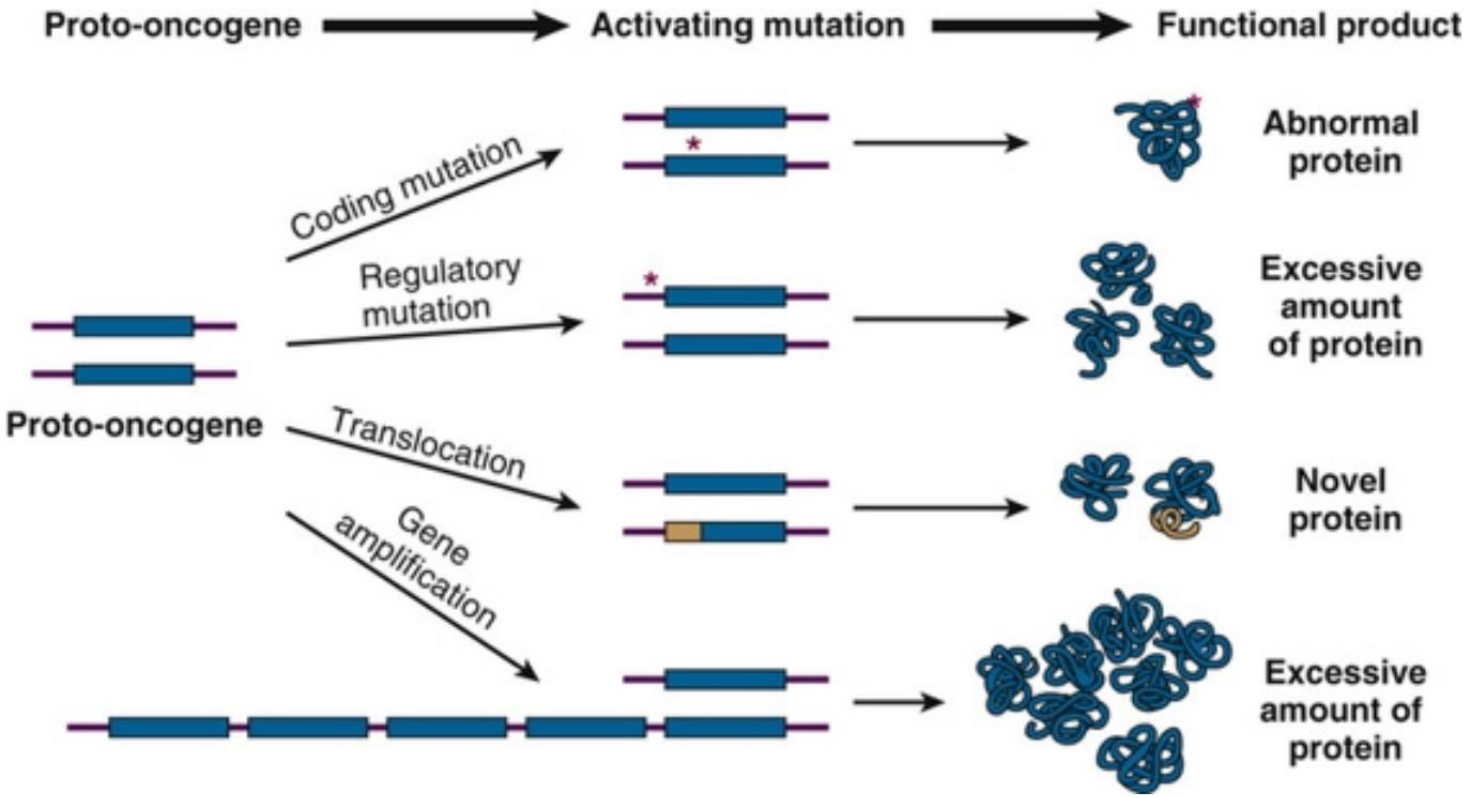
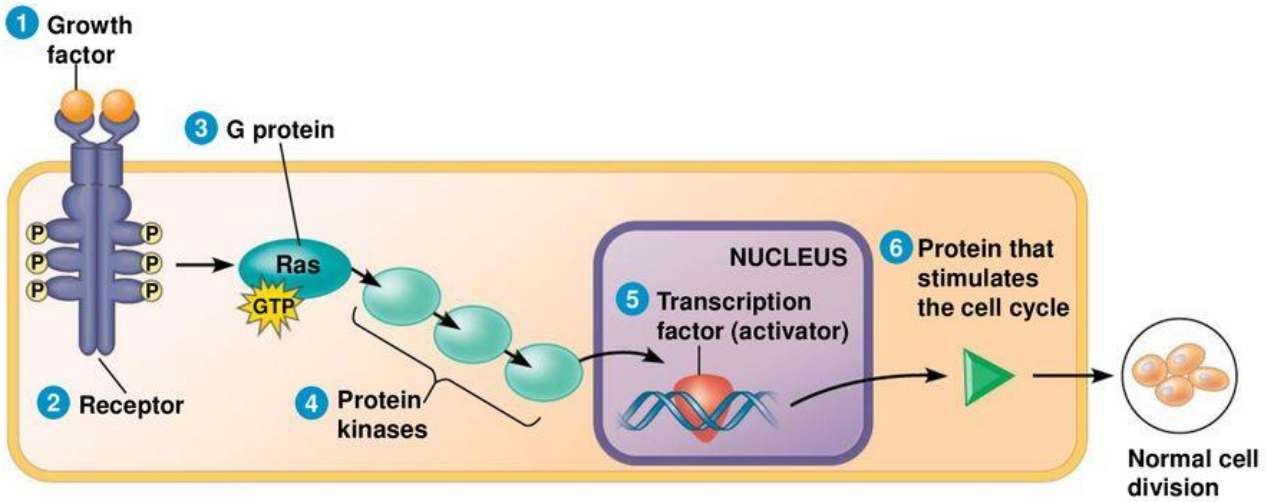


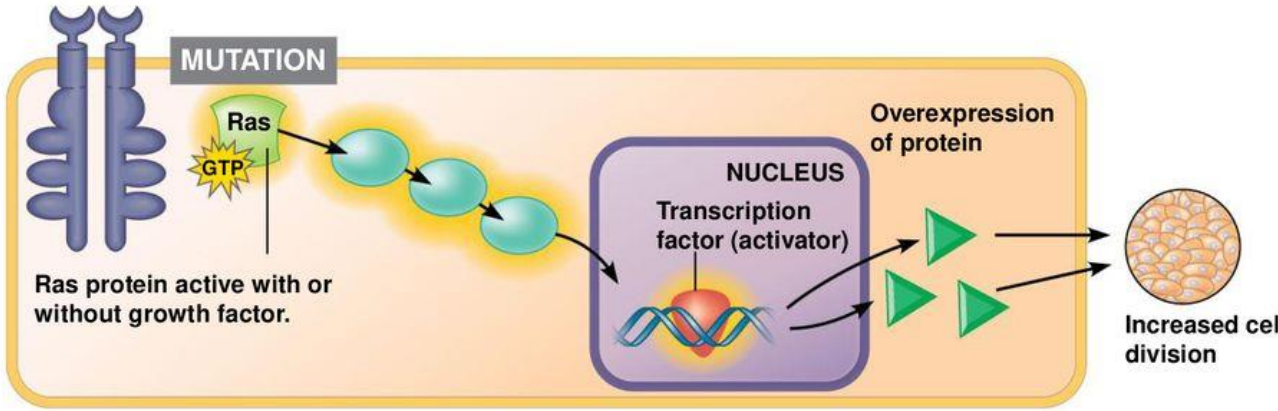
FIGURE 15-3 Different mutational mechanisms leading to proto-oncogene activation. These include a single point mutation leading to an amino acid change that alters protein function, mutations or translocations that increase expression of an oncogene, a chromosome translocation that produces a novel product with oncogenic properties, and gene amplification leading to excessive amounts of the gene product.

Oncogenes encode proteins such as the following:

- Proteins in signaling pathways for cell proliferation
- Transcription factors that control the expression of growth-promoting genes
- Inhibitors of programmed cell death machinery



Normal cell cycle–stimulating pathway.

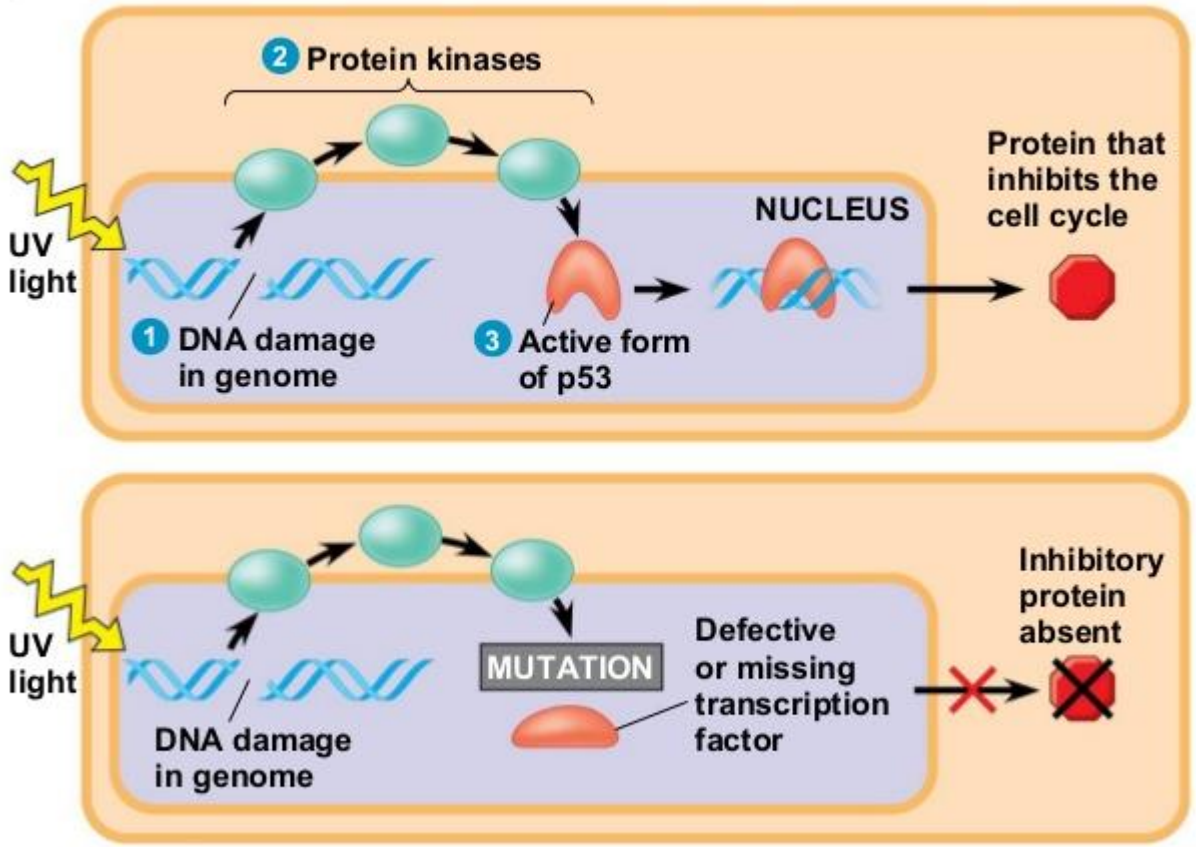


Mutant cell cycle–stimulating pathway.

The second, and more common, category of driver genes includes tumor suppressor genes (**TSGs**), variants in which cause a *loss of expression* of proteins necessary to control the development of cancers.

To drive oncogenesis, loss of function of a TSG typically requires mutations at both alleles.

Figure 16.18



Loss-of-function mechanisms can range from missense, nonsense, or frame-shift mutations to gene deletions or loss of a part or even an entire chromosome.

Loss of function of TSGs can also result from epigenomic transcriptional silencing due to:

- altered chromatin conformation
- promoter methylation
- translational silencing by miRNAs or disturbances in other components of the translational machinery

TSGs encode proteins involved in many aspects of cellular function, including but not limited to:

- maintenance of correct chromosome number and structure
- DNA repair proteins
- proteins involved in regulating the cell cycle, cellular proliferation, or contact inhibition

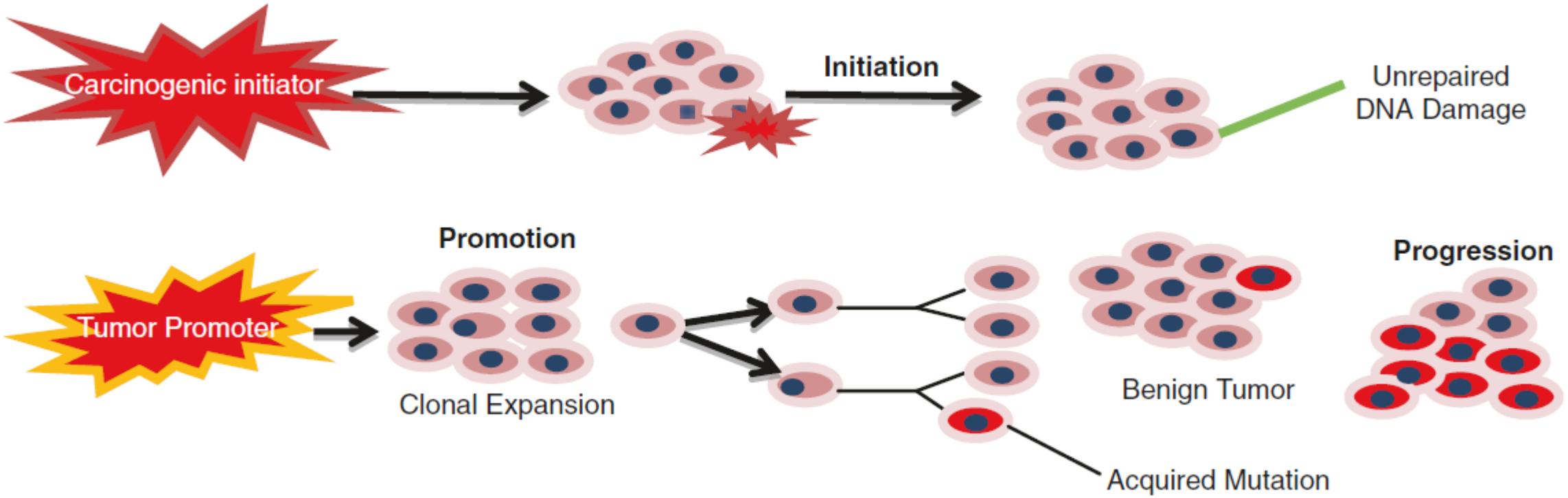
Cellular Heterogeneity within Individual Tumors

The accumulation of driver gene mutations does not occur synchronously, in lockstep, in every cell of a tumor.

To the contrary, cancer evolves along multiple lineages within a tumor

mutational and epigenetic events in different cells activate proto-oncogenes and cripple the machinery for maintaining genome integrity, leading to more genetic changes in a vicious cycle of more mutations and worsening growth control.

The lineages that experience an enhancement of growth, survival, invasion, and distant spread will come to predominate as the cancer evolves and progresses



A paradigm for the development of cancer

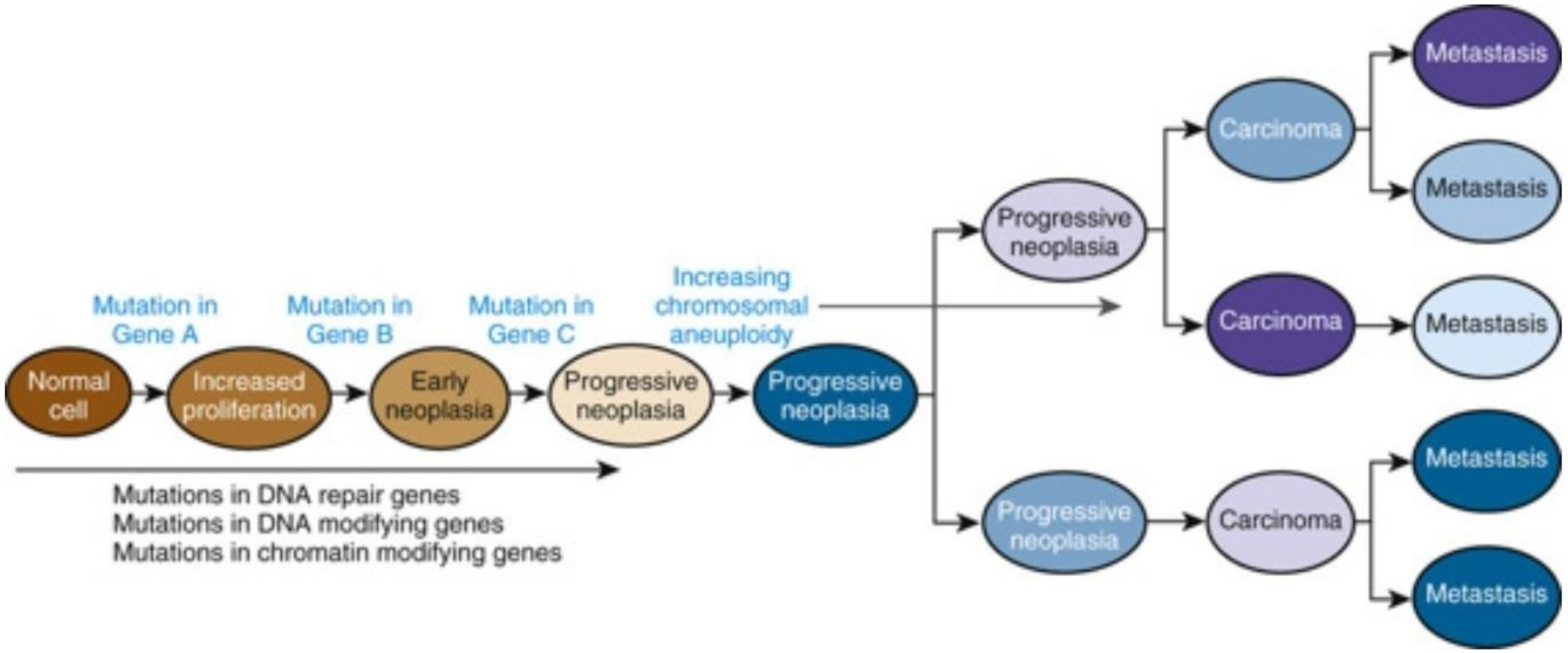


FIGURE 15-4 **Stages in the evolution of cancer. Increasing degrees of abnormality are associated with sequential loss of tumor suppressor genes from several chromosomes and activation of proto-oncogenes, with or without a concomitant defect in DNA repair. Multiple lineages, carrying different mutations and epigenomic profiles, occur within the primary tumor itself, between the primary and metastases and between different metastases.**

the original clone of neoplastic cells evolves and gives rise to multiple sublineages

each carrying a set of mutations and epigenomic alterations that are different from but overlap with what is carried in other sublineages.

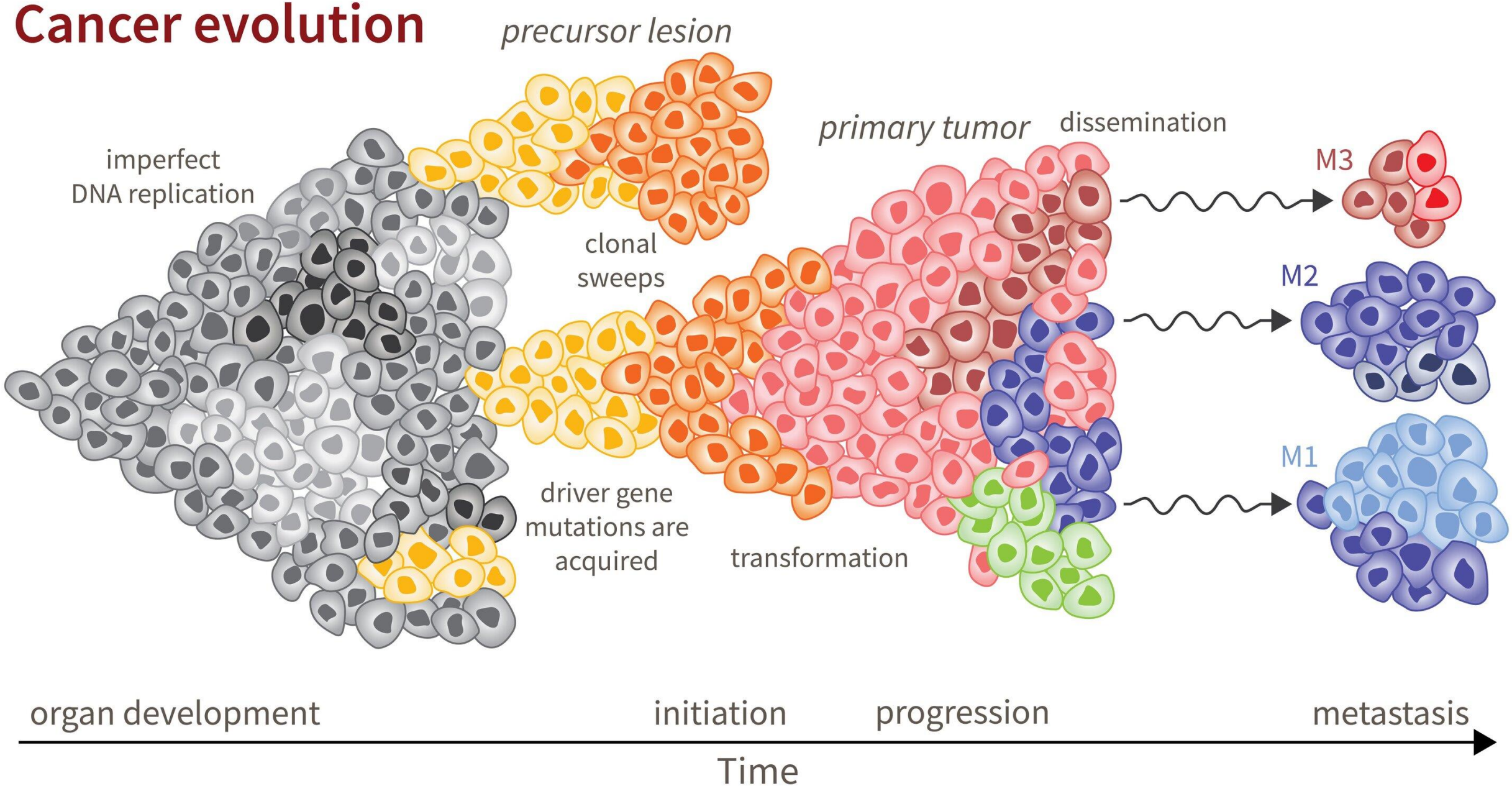
The profile of mutations and epigenomic changes can differ:

Between the primary and its metastases

Between different metastases,

Between the cells of the original tumor or within a single metastasis.

Cancer evolution



Cancer in Families

hereditary cancer syndromes follow mendelian patterns of inheritance, where increased incidence is due primarily to inheritance of a single mutant gene with high penetrance.

approximately 100 different genes in which deleterious mutations increase the risk for cancer many-fold higher than in the general population
https://www.invitae.com/en/physician/tests/01101/

There are also many dozens of additional genetic disorders that are not usually considered to be hereditary cancer syndromes and yet include some increased predisposition to cancer (for example, the ten- to twenty-fold increased lifetime risk for leukemia in Down syndrome

Cancer in Families

Not all families with an apparently increased incidence of cancer can be explained by known mendelian or clearly recognized genetic disorders.
These families likely represent the effects of both shared environment and one or more genetic variants that increase susceptibility and are therefore classified as **multifactorial**, with complex inheritance.

Although individuals with a *hereditary cancer syndrome represent ~ 5%* of all patients with cancer, identification of a genetic basis for their disease has great importance both for clinical management of these families and for understanding cancer in general.

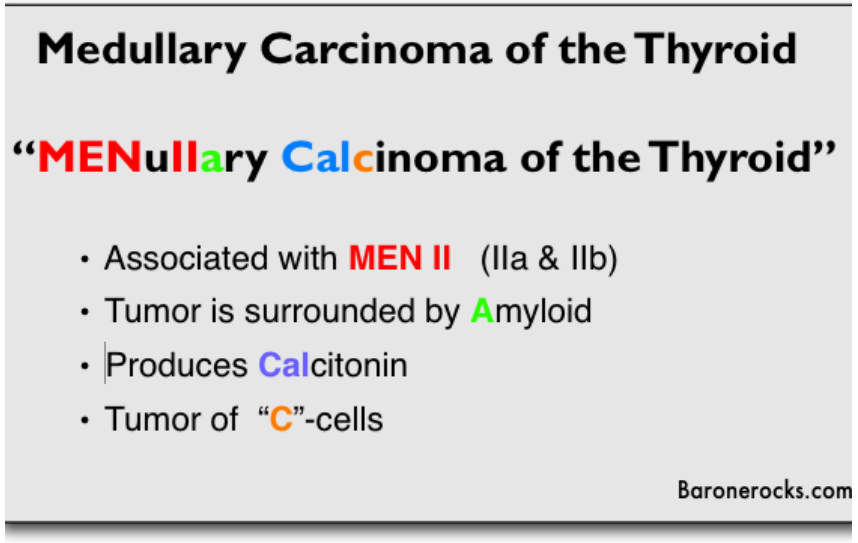
Activated Oncogenes in Hereditary Cancer Syndromes

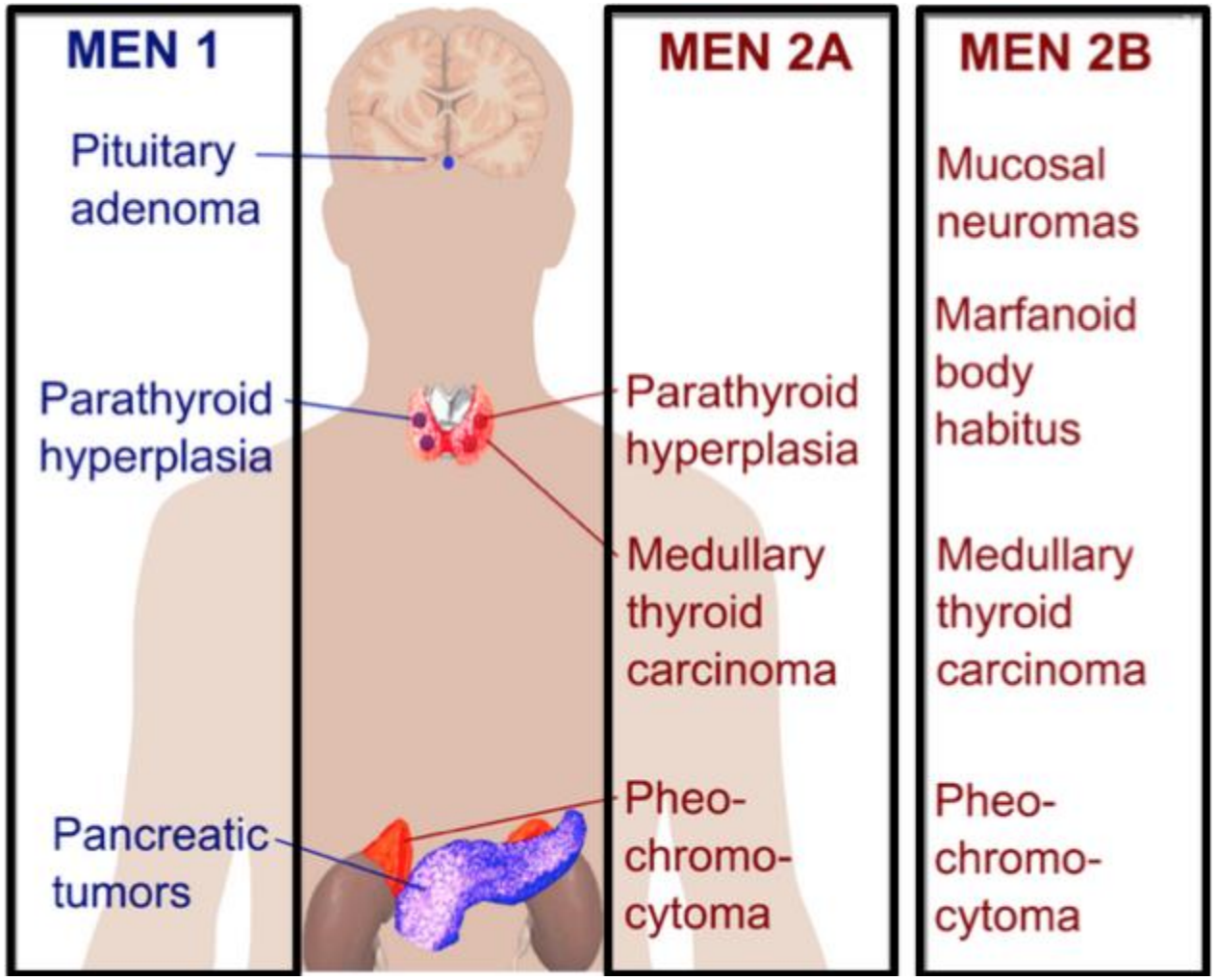
Multiple Endocrine Adenomatosis, Type 2

Adenomatosis: An abnormal overgrowth of, or TUMOUR formation in, two or more of the ENDOCRINE glands

MEN2-A is an AD disorder characterized by:
high incidence of medullary carcinoma of the thyroid that is often but not always associated with
pheochromocytoma,
benign parathyroid adenomas, or both.

Pheochromocytoma: is a rare, usually noncancerous (benign) tumor that develops in an adrenal gland.



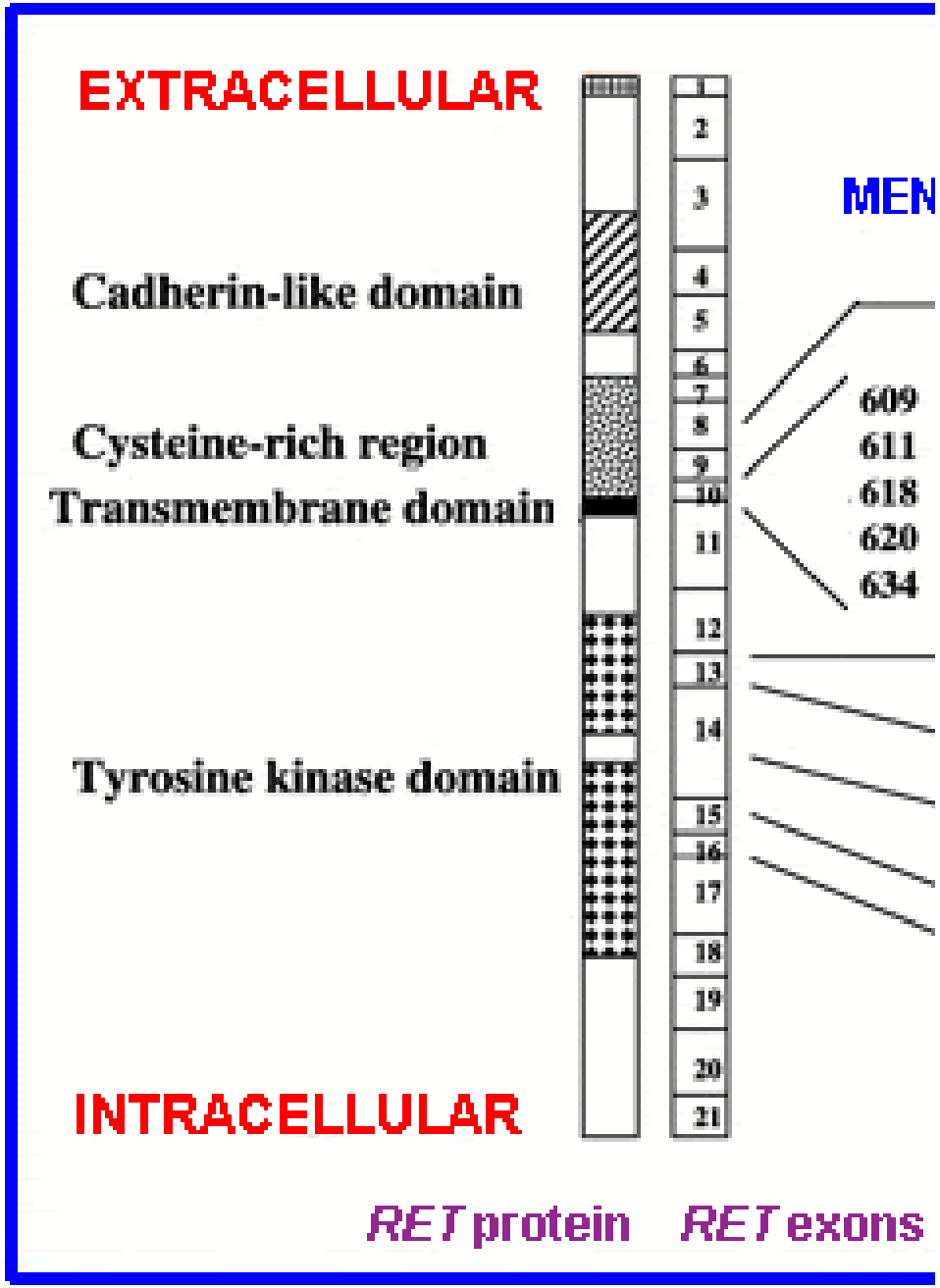


Patients with the rarer type B variant, **MEN2B**, have, in addition to the tumors seen in patients with MEN2A,
thickening of nerves and the development of benign neural tumors, known as **neuromas**, on the mucosal surface of the mouth and lips and along the gGI tract.

The variants responsible for MEN2 are in the *RET* gene

Individuals who inherit an activating mutation in *RET* have a greater than 60% chance of developing a particular type of thyroid carcinoma (medullary)

More sensitive tests, such as blood tests for thyrocalcitonin or urinary catecholamines synthesized by pheochromocytomas, are abnormal in well above 90% of heterozygotes for MEN2



RET encodes a cell-surface protein that contains:

- **extracellular domain** that can bind signaling molecules
- **cytoplasmic** tyrosine kinase domain

Tyrosine kinases are a class of enzymes that phosphorylate tyrosines in proteins.
Tyrosine phosphorylation initiates a signaling cascade changes in protein-protein and DNA-protein interactions and in the enzymatic activity of many proteins

Normally, tyrosine kinase receptors must bind specifi signaling molecules in order to undergo the conformational change that makes them enzymatical active and able to phosphorylate other cellular protei

The mutations in RET that cause MEN2A increase its kinase activity even in the absence of its ligand (a stat referred to as
constitutive activation

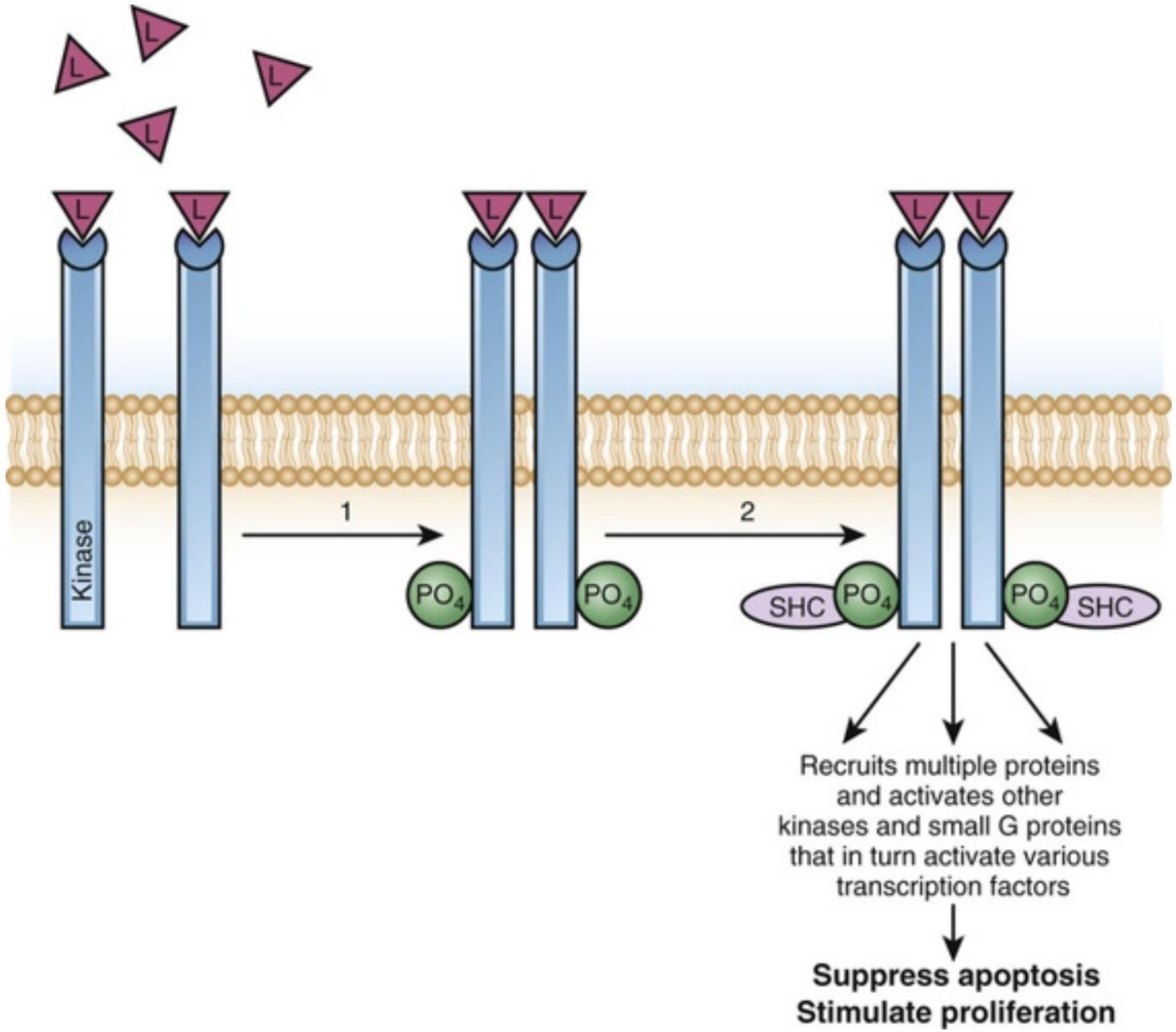
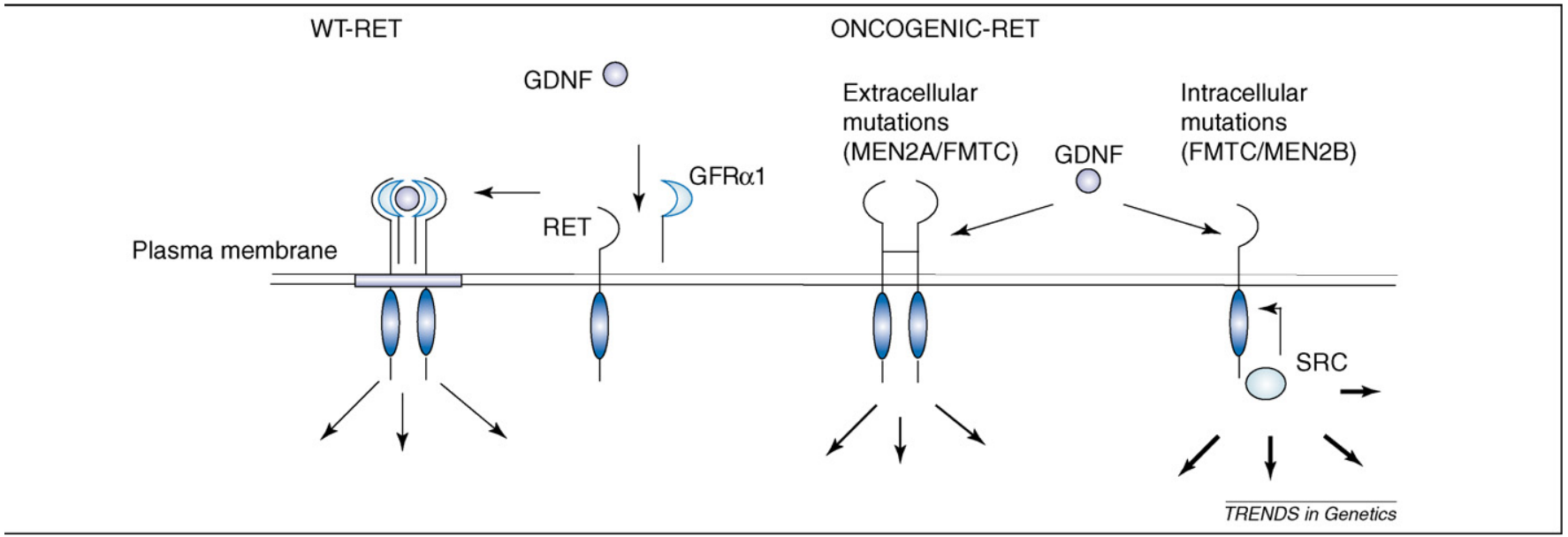


FIGURE 15-5 Schematic diagram of the function of the Ret receptor, the product of the *RET* proto-oncogene. Upon binding of a ligand (L), such as glial-derived growth factor or neurturin, to the extracellular domain, the protein

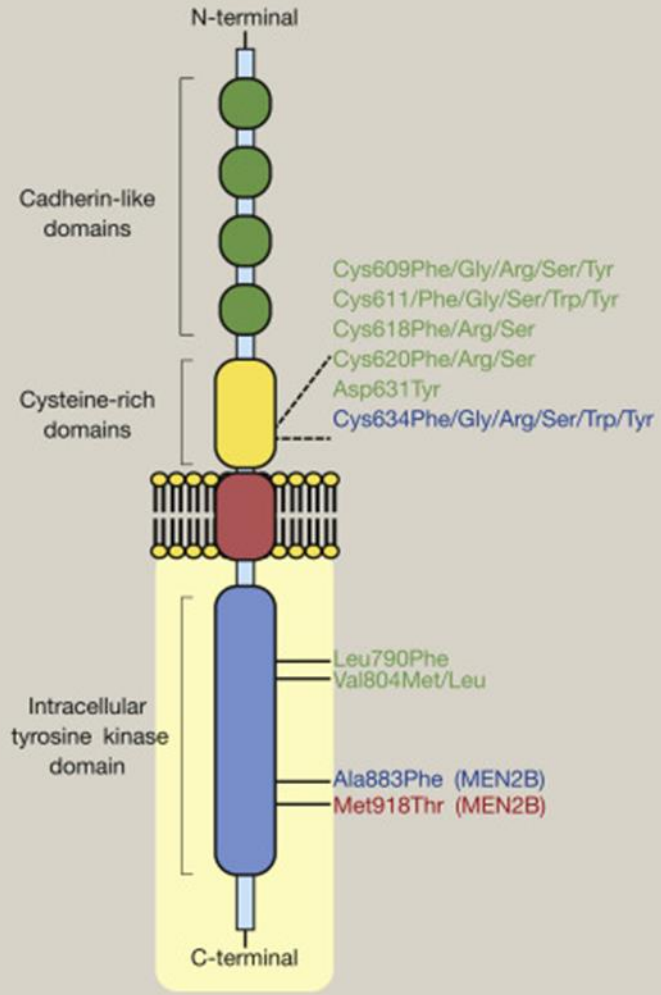
The RET gene is expressed in many tissues of the body and is required for normal embryonic development of autonomic ganglia and kidney.

It is unclear why germline activating mutations in this proto-oncogene result in a particular cancer of distinct histological types restricted to specific tissues,
whereas other tissues in which the oncogene is expressed do not develop tumors.



re 5. Possible mechanisms of activation of wild-type RET and MEN2-associated *RET* mutations. **(a)** Activation of wild-type RET: the ligand (GDNF) first binds to the GPI-
or co-receptor 1 (GFRα1); RET is then recruited to form a macromolecular complex receptor. **(b)** Constitutive activation of RET by mutations affecting the cysteine-rich
ain that cause covalent dimerization of the (mutant) receptor. **(c)** Aberrant activation of mutations affecting the tyrosine kinase domain of RET, resulting in monomeric
proteins with altered catalytic activity and altered substrate specificity that preferentially recognize substrates of cytoplasmic tyrosine kinases such as SRC or ABL.

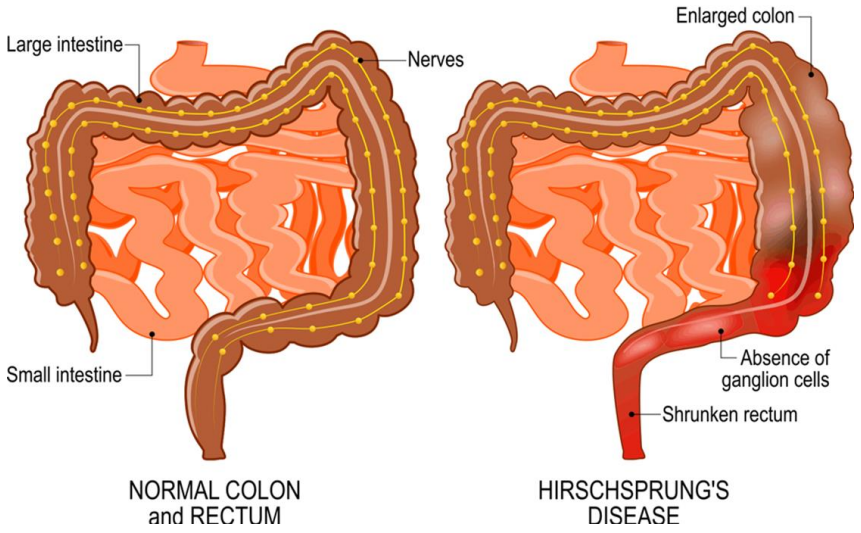
RET receptor structure and location of common MEN2-associated *RET* mutations



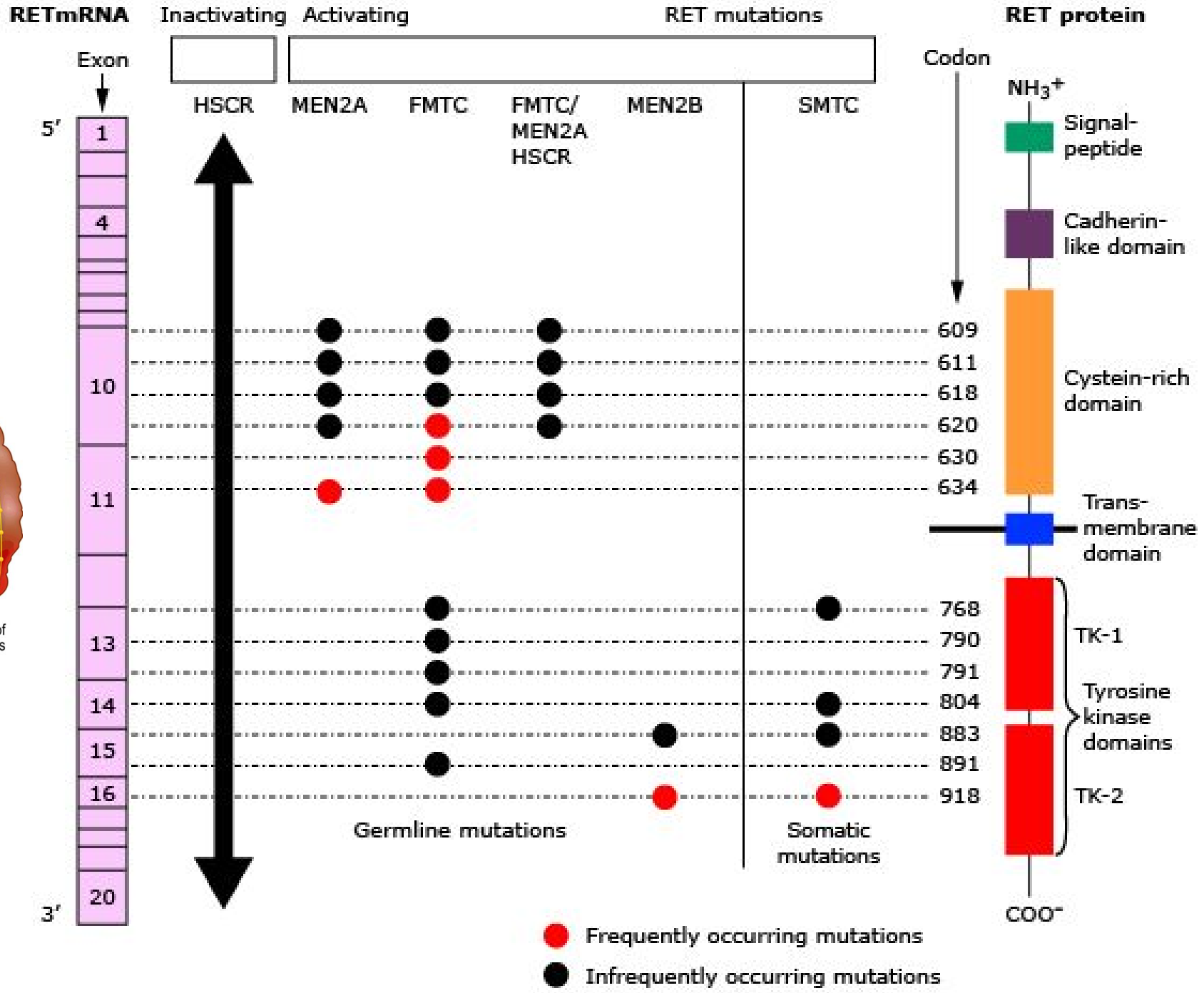
The RET receptor is a membrane-associated tyrosine kinase receptor expressed in cells of neural crest origin. MEN2-associated mutations arise most frequently in the cysteine-rich region of the extracellular domain, or in the intracellular domain associated with intrinsic tyrosine kinase activity, resulting in enhanced receptor signalling. *RET* mutations are described according to the respective missense substitution, with amino acids represented using standard nomencalture. The American Thyroid Association[5] risk category of each *RET* mutation is represented by colour; red, 'highest' risk; blue, 'high' risk; green, 'moderate 'risk. Mutations associated with MEN2B are noted in parentheses.

Gain of function vs loss of function

Interestingly, RET is the same gene implicated in Hirschsprung disease, although those mutations are usually loss-of-function, not activating, mutations.



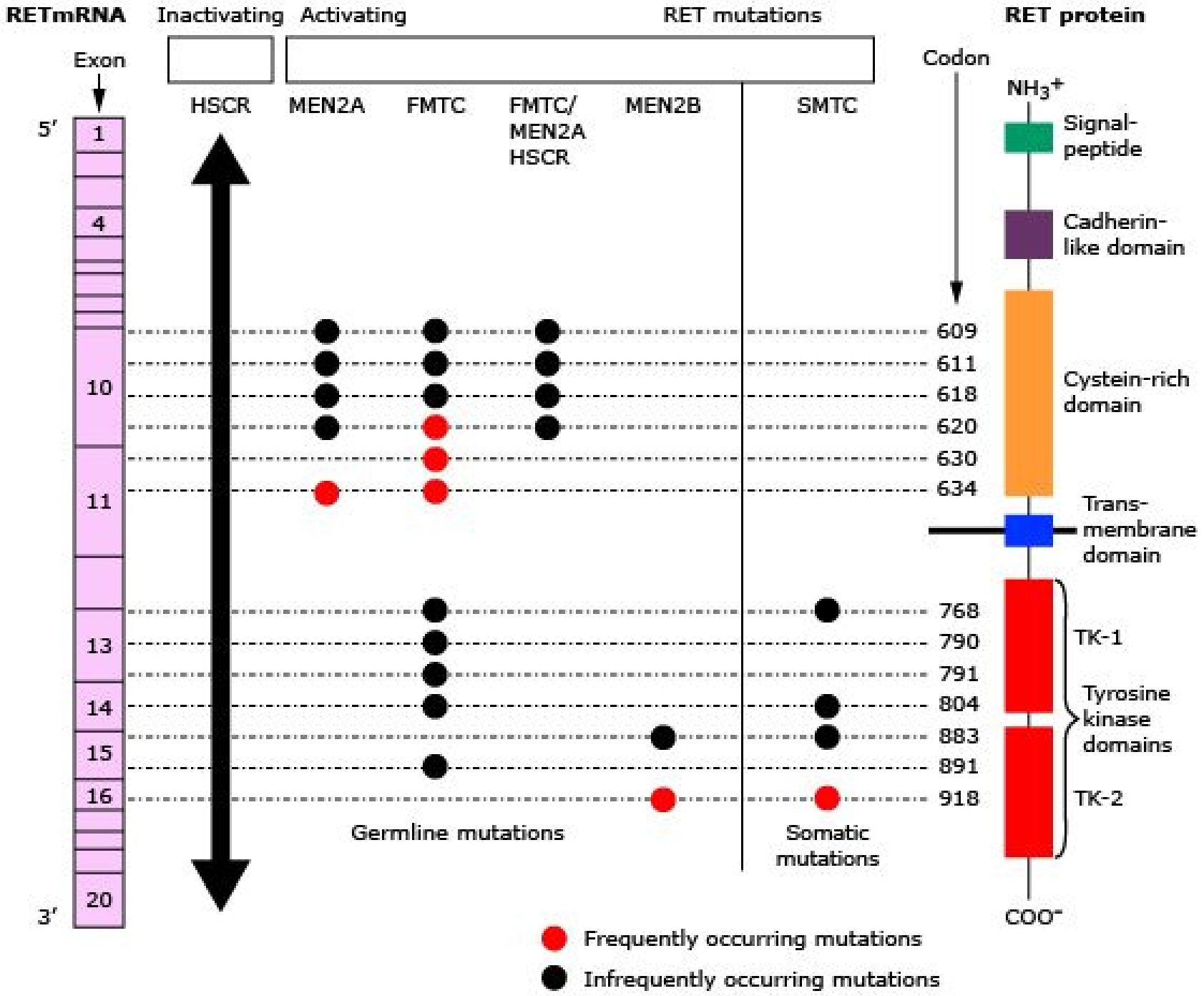
HSCR: Hirschsprung disease
MEN: Multiple endocrine neoplasia
FMTC: Familial medullary thyroid cancer
SMTC: Sporadic medullary thyroid cancer



Gain of function vs loss of function

There are, however, some families in which the same mutation in RET can act as an activated oncogene in some tissues (such as thyroid) and cause MEN2A, while not having sufficient function in other tissues, such as the developing enteric neurons of the gastrointestinal tract, resulting in Hirschsprung disease.

Thus even the identical mutation can have different effects on different tissues.



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