Genetics of Cancer

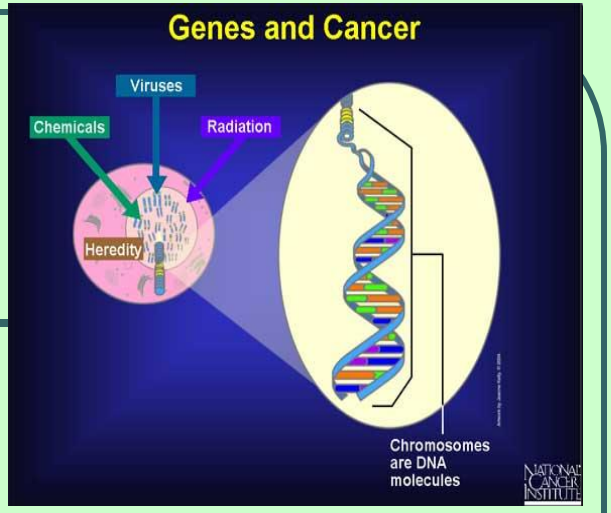
Cancer

- Cancer is not a single disease - great variety of malignant tumors that are formed by the same basic process of uncontrolled growth.
- Many aspects of cell function are controlled by a balance of positive and negative signals received from inside and outside the cell. In tumor, the balance between cell proliferation and cell death is lost.
- Cancer has both genetic and environmental causes.

The Genetic Nature of Cancer

- Nearly all cancers are caused by abnormalities in the genetic material of the transformed cell.
- In order for a normal cell to transform into a cancer cell , genes which regulate cell growth and differentiation must be altered. When normal regulation is altered, uncontrolled growth is initiated and a malignant tumor develop.

Causes of cancer

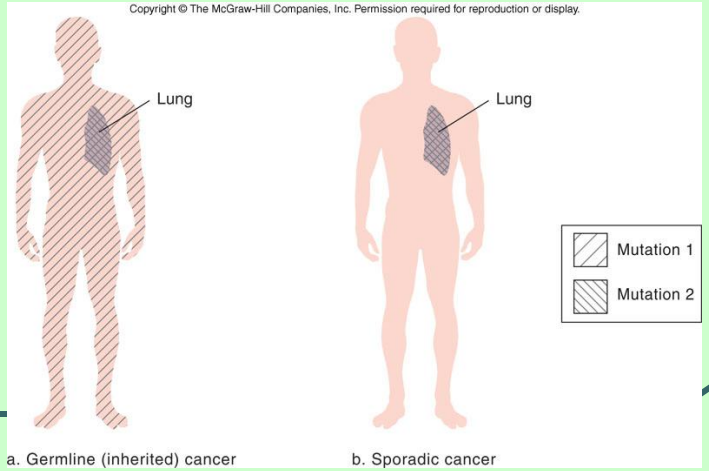


- Carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents (Viruses are involved in cancers) .
- Randomly acquired through errors in DNA replication or
- Inherited and thus present in all cells from birth.

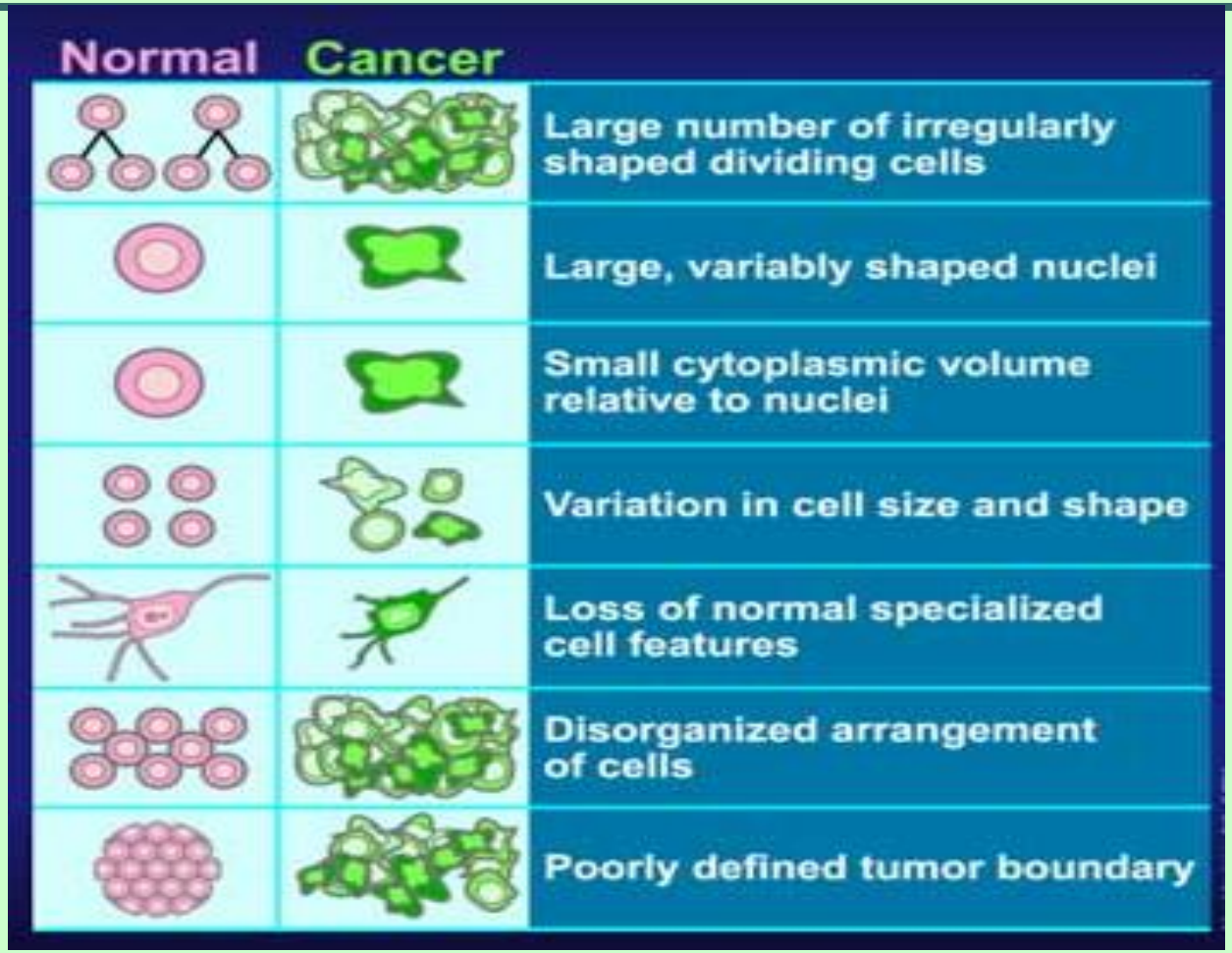
There are two basic kinds of genetic mutations

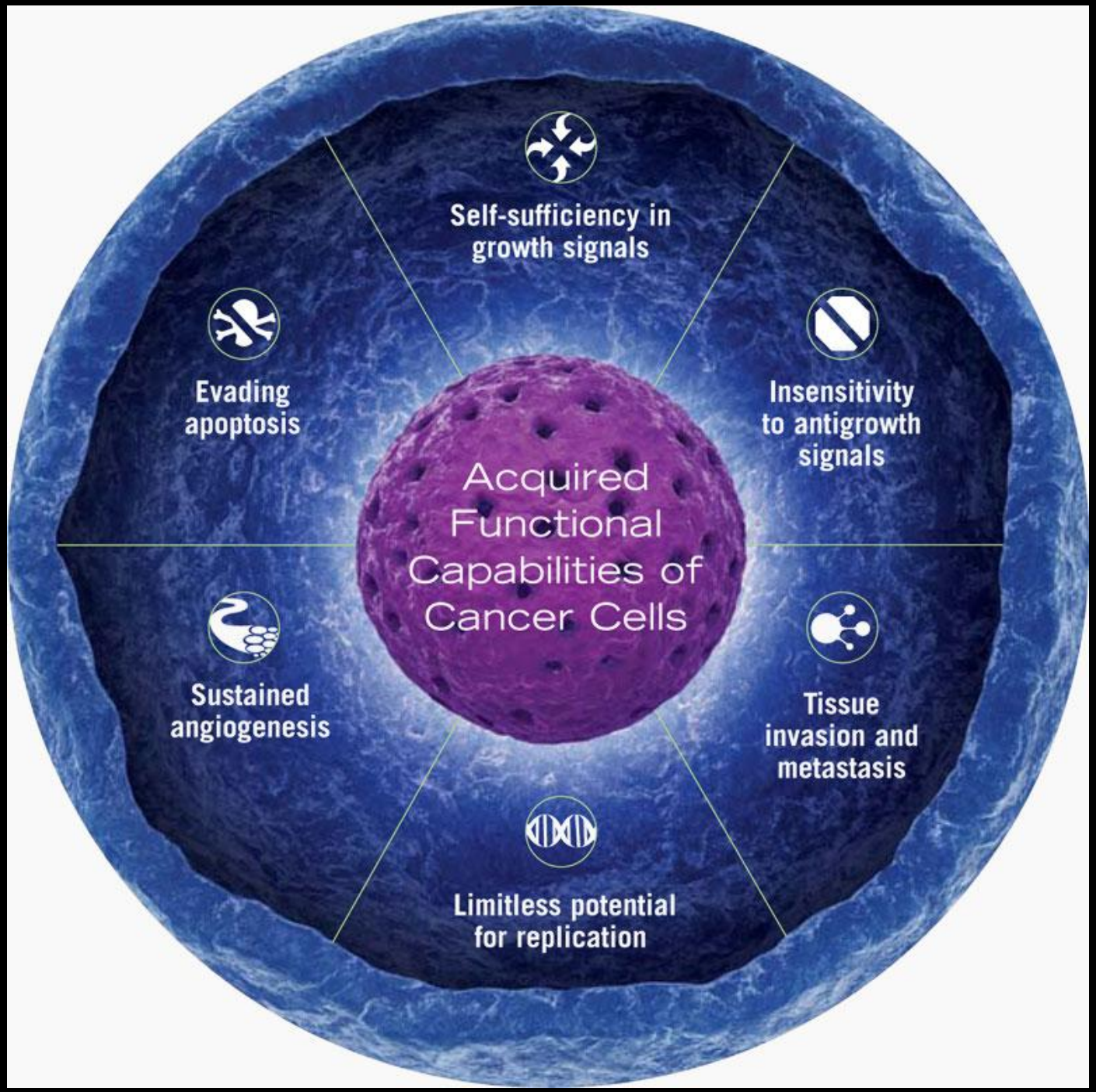
- Germline mutations are mutations that are inherited (usually require second somatic mutation), also called familial (occurring in families) cancer.

- Sporadic cancer or somatic mutation. Most cancers are caused by a series of mutations that develop during a person's lifetime called acquired mutations. These mutations are not in every cell of the body and are not passed from parent to child.



Microscopic Appearance of Cancer Cells




Self-sufficiency in growth signals
Insensitivity to antigrowth signals
Tissue invasion and metastasis
Limitless potential for replication
Sustained angiogenesis
Evading apoptosis
Acquired Functional Capabilities of Cancer Cells

Genes That play a Role in Cancer

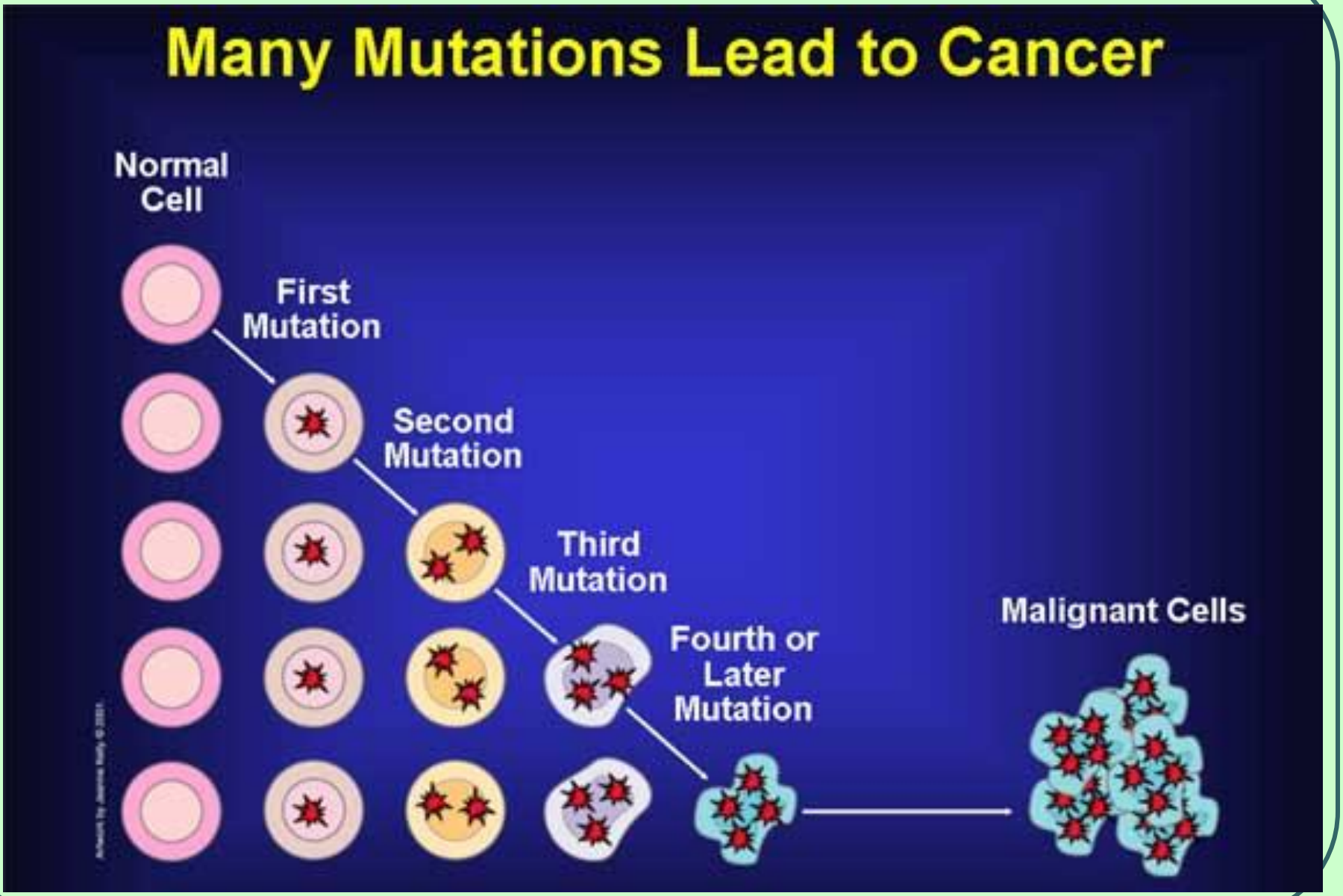
- **Oncogenes**
- **Tumor suppressor genes**
- **DNA repair genes. These are genes that fix any mistakes made when DNA is replicated (copied). Mistakes that aren't fixed become mutations, which may eventually lead to cancer.**

The two types have opposite effects in carcinogenesis.

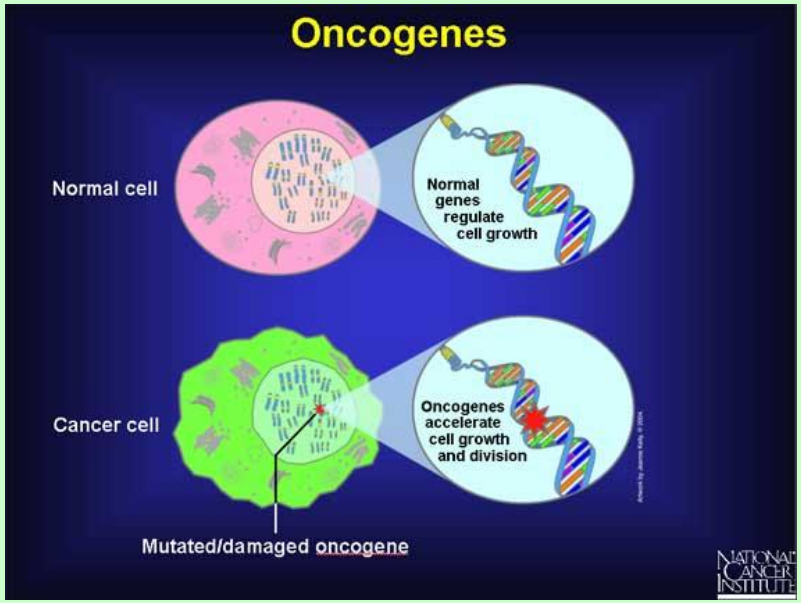
Oncogenes facilitate malignant transformation, whereas tumor suppressor genes, block tumor development by regulating genes involved in cell growth.

Some Genes Associated with Cancer

NAME	FUNCTION	EXAMPLES of Cancer/Diseases	TYPE of Cancer Gene
APC	regulates transcription of target genes	Familial Adenomatous Polyposis	tumor suppressor
BCL2	involved in apoptosis; stimulates angiogenesis	Leukemia; Lymphoma	oncogene
BLM	DNA repair	Bloom Syndrome	DNA repair
BRCA1	may be involved in cell cycle control	Breast, Ovarian, Prostatic, & Colonic Neoplasms	tumor suppressor
BRCA2	DNA repair	Breast & Pancreatic Neoplasms; Leukemia	tumor suppressor
HER2	tyrosine kinase; growth factor receptor	Breast, Ovarian Neoplasms	oncogene
MYC	involved in protein-protein interactions with various cellular factors	Burkitt's Lymphoma	oncogene
p16	cyclin-dependent kinase inhibitor	Leukemia; Melanoma; Multiple Myeloma; Pancreatic Neoplasms	tumor suppressor
p21	cyclin-dependent kinase inhibitor		tumor suppressor
p53	apoptosis; transcription factor	Colorectal Neoplasms; Li-Fraumeni Syndrome	tumor suppressor
RAS	GTP-binding protein; important in signal transduction cascade	Pancreatic, Colorectal, Bladder Breast, Kidney, & Lung Neoplasms; Leukemia; Melanoma	oncogene
RB	regulation of cell cycle	Retinoblastoma	tumor suppressor
SIS	growth factor	Dermatofibrosarcoma; Meningioma; Skin Neoplasms	oncogene
XP	DNA repair	Xeroderma pigmentosum	DNA repair


Many Mutations Lead to Cancer
Normal Cell
First Mutation
Second Mutation
Third Mutation
Fourth or Later Mutation
Malignant Cells

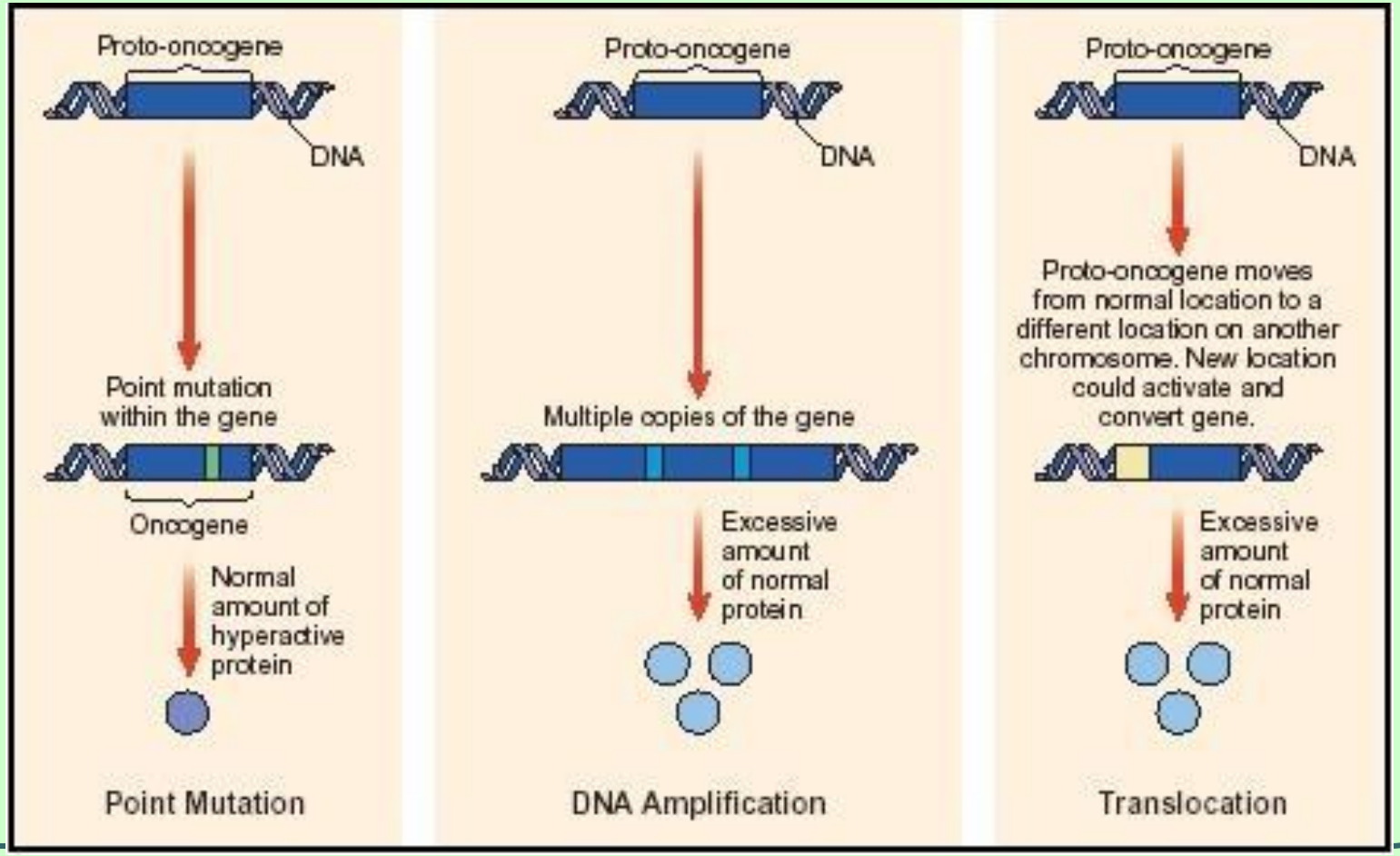
Proto-oncogene



- proto-oncogene is a normal gene that can become an oncogene due to mutations or increased expression
- Proto-oncogenes code for proteins that help to regulate cell growth and differentiation
- often involved in signal transduction and execution of mitogenic signals

e.g. *myc ,abl, ras*

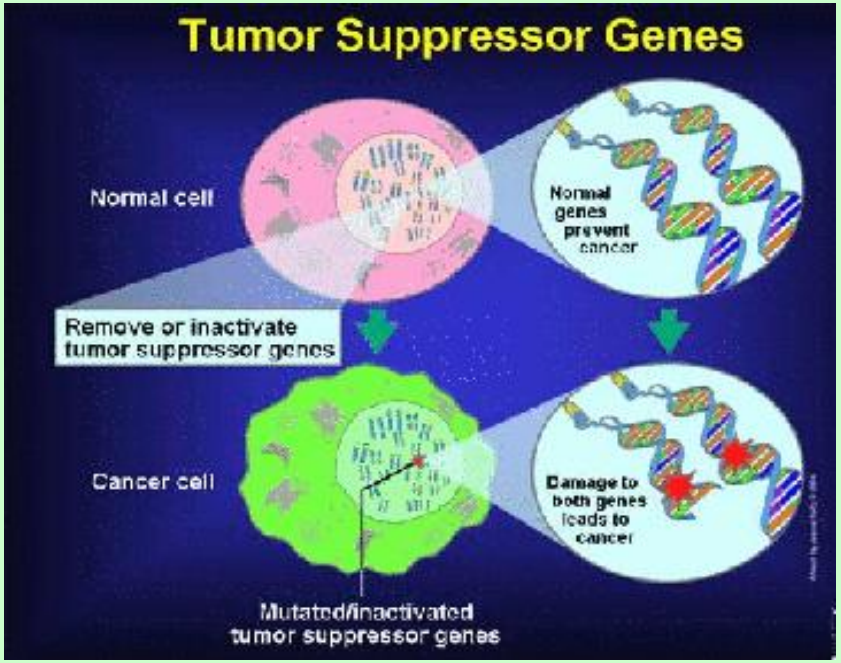
Activation of Proto-oncogene



Tumor Suppressor Genes

Tumor suppressor gene or anti oncogene: In contrast to oncogene, tumor suppressor genes are normal genes implicated in the control of cell cycle, repair DNA mistakes, and tell cells when to die (apoptosis or programmed cell death).

When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.



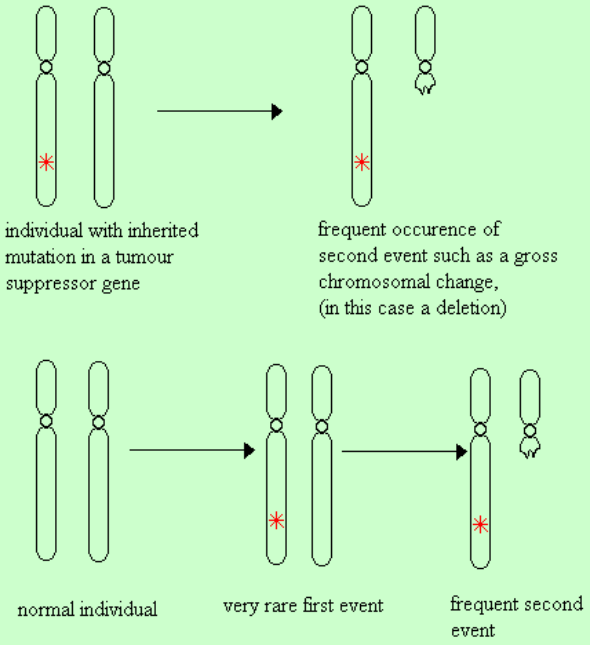
Types of Tumor Suppressor Genes

- **Genes that control cell division** : Some tumor suppressor genes help control cell growth and reproduction, e.g. retinoblastoma (Rb1)

- **Genes that repair DNA**:The genes responsible for HNPCC (hereditary nonpolyposis colon cancer) are examples of DNA repair gene defects. When these genes do not repair the errors in DNA, HNPCC can result.

- **Cell "suicide" genes** : If there is too much damage to a cell's DNA to be fixed by the DNA repair genes, the *p53* tumor suppressor gene is responsible for destroying the cell by a process sometimes described as "cell suicide."

Knudsen's "two hit" hypothesis



- Two mutations are required
  - One in each copy of the RB gene
- For sporadic cases
  - Retinoblastoma is a result of two somatic mutations – unilateral form
  - 60% pacients, later manifestation (24 months)
- For familial cases
  - Retinoblastoma is inherited as an autosomal recessive mutation
  - bilateral/multifocal form
  - 40% pacients, earlier development (8 months)
  - Followed by a somatic mutation in the normal allele.
  - The chance of a second somatic mutation is high
  - Creates a dominant "susceptibility" to cancer in the family

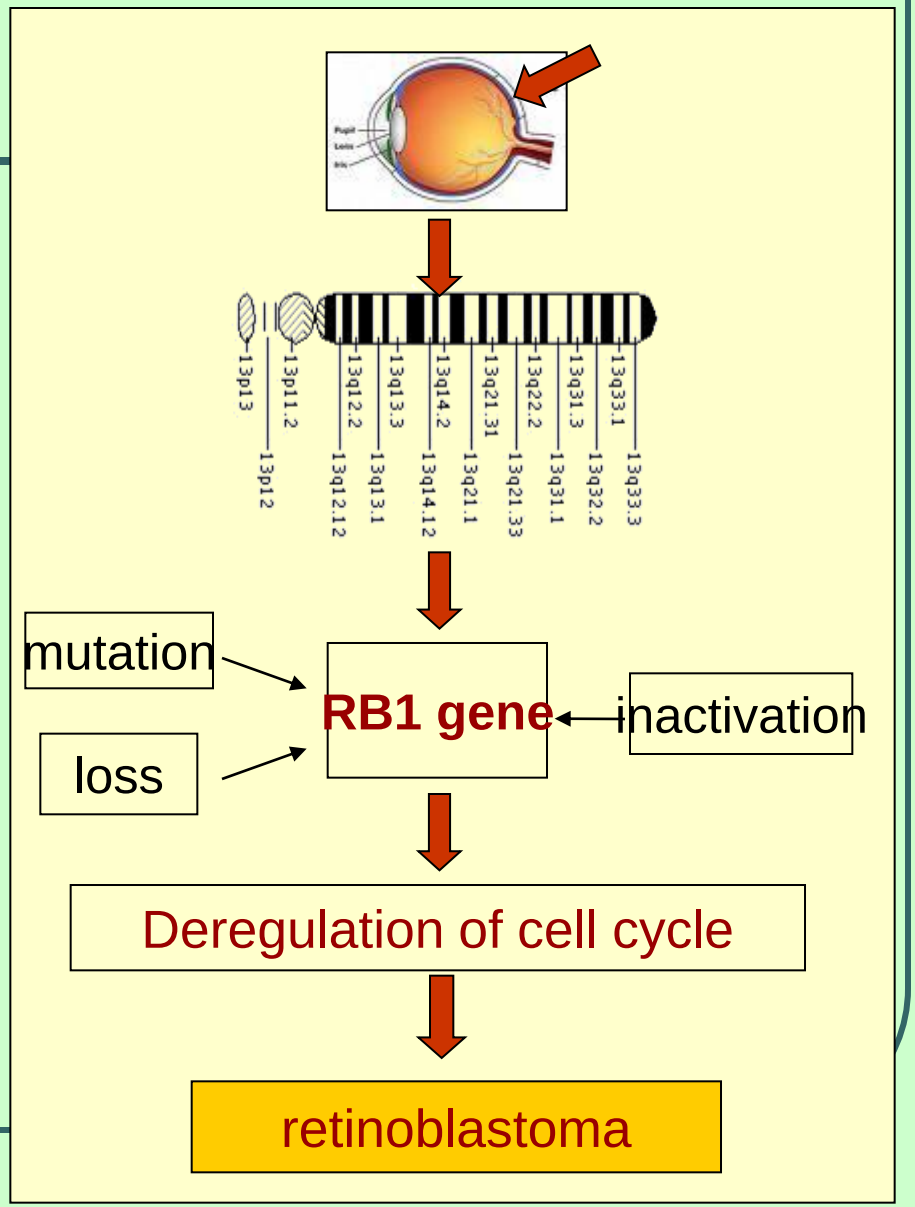
retinoblastoma

- **Retinoblastoma** (RB) is a malignant tumor of the developing retina of children, usually before the age of five years.
- mutation in the gene *RB1* located on chromosome 13
- The gene is about 180 kb in length with 27 exons that code for a transcript of only 4.7 kb.
- individual mutations are heterogeneous: 20% are deletions larger than 1kb; 30% are small deletions or insertions; 45% are point mutations.

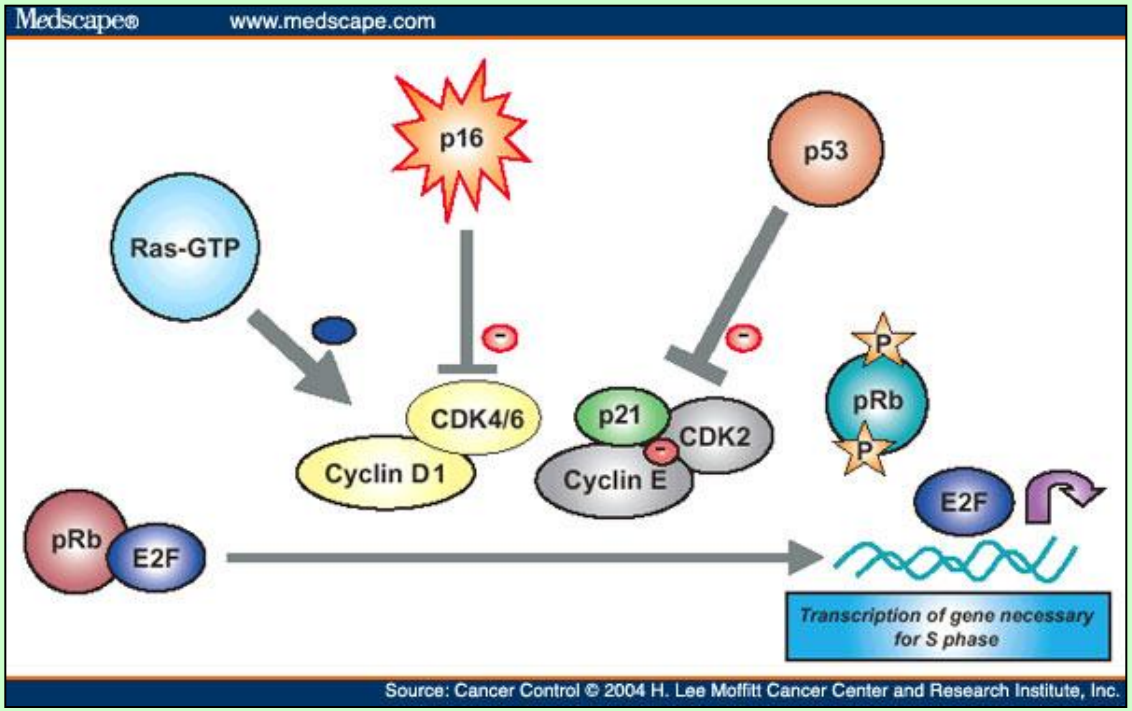


Gene RB1

- localisation - 13q14.1-14.2
- 27 exons,
  >180kb genomic DNA
- tumor-supressor activity



Retinoblastoma protein (pRb) - function



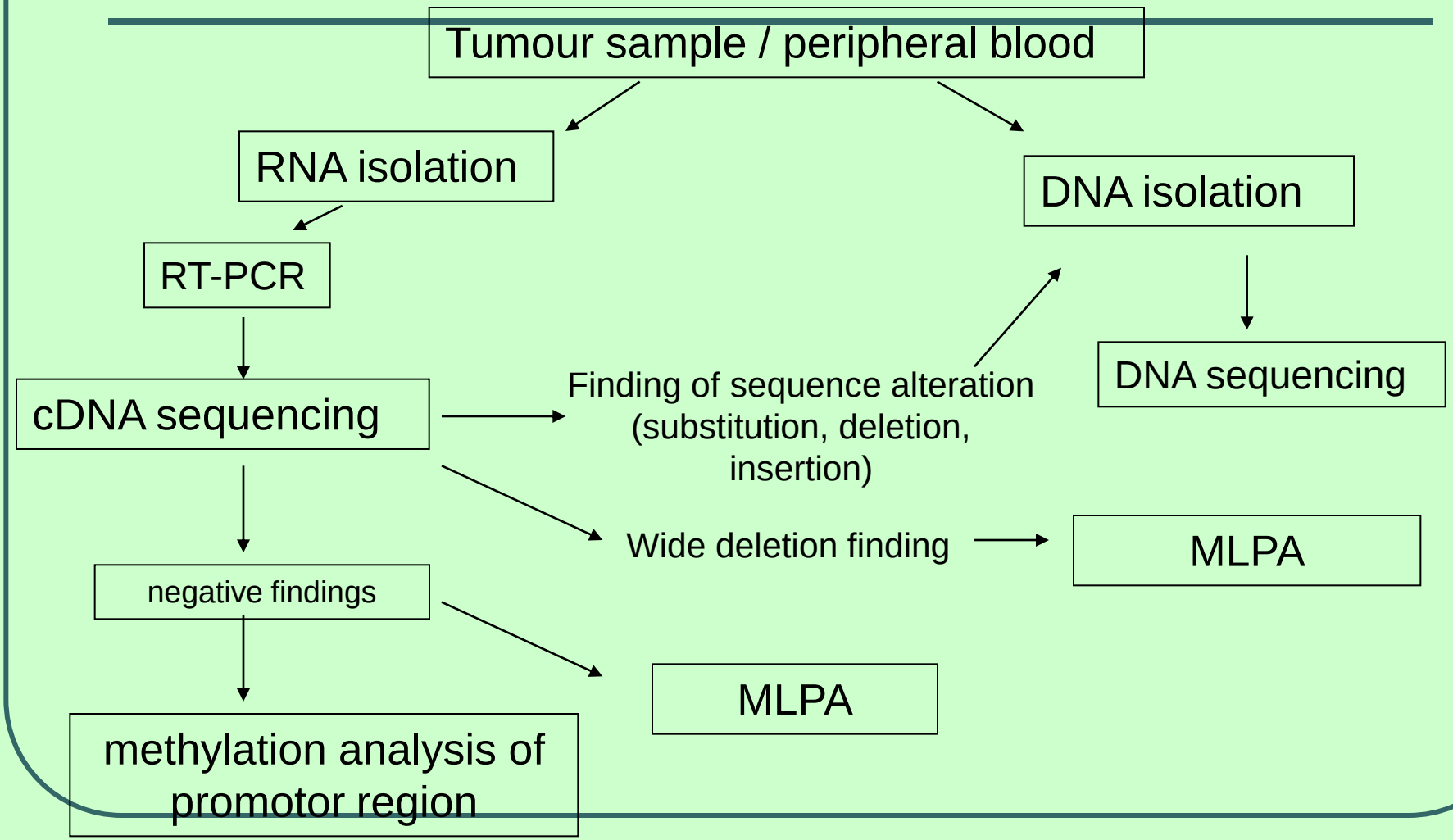
•**<u>Cell cycle „brake“ – control point for transition from</u>** <u>G1 to S phase:</u>

- pRb in active form binds transcription factor E2F
- CyklinD- and CyklinE-dependent kinases phosphorylate and inactivate pRb
- inactive pRb releases E2F transcription factors,which stimulate expression of cyclins and other genes needed for DNA synthesis and transition to S phase

Molecular genetic analysis of Rb1 gene

- Described more than 500 mutations
- Spread over whole coding region
- **Different forms of Rb1 inactivation lead to different penetration and expressivity and thus to various clinical manifestations of disease**
- Hereditary vs sporadic form

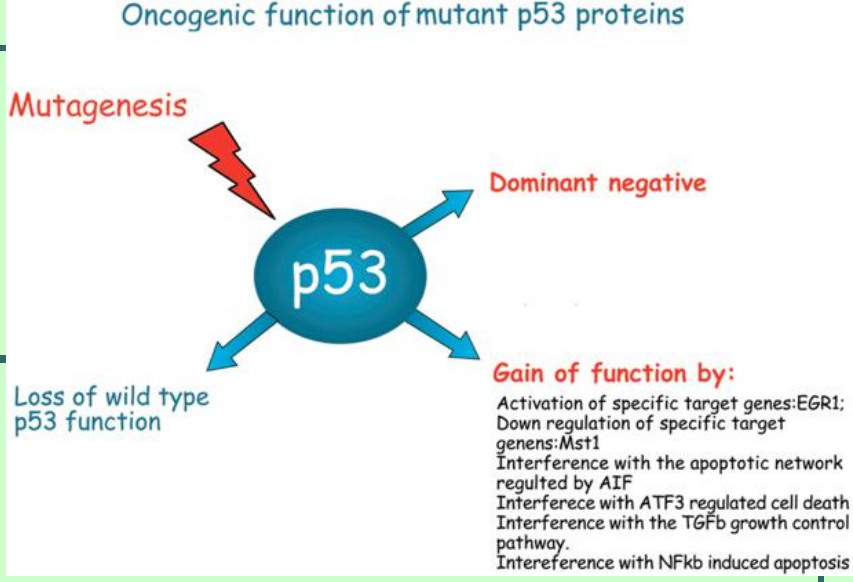
Strategy of molecular analysis of RB1 gene



Metylation analysis of promotor

- Hypermetylation of CpG islands in promotor region lead to repression of transcription – gene silencing
- In tumour supresor genes (RB1, BRCA1, p15, p16..) hypermetylation of promotors is one of mechanisms of oncogenesis

p53



- suppresses progression through the cell cycle in response to DNA damage
- initiates apoptosis if the damage to the cell is severe
- acts as a tumour suppressor
- is a transcription factor, represses transcription of one set of genes (several of which are involved in stimulating cell growth) while stimulating expression of other genes involved in cell cycle control
- Determines if a cell has repaired DNA damage
- If damage cannot be repaired, p53 can induce apoptosis
- More that 50% of human cancers involve an abnormal p53 gene

Inherited Abnormalities of Tumor Suppressor Genes - in several cancers that tend to run in families.

- p53, RB1, genes involved in HNPCC
- *APC* gene causes *familial polyposis* – colon polyps
- *BRCA* - breast cancers.

Non-inherited mutations of tumor suppressor genes : Acquired mutations (those which happen during a person's life).

The p53 gene is believed to be among the most frequently mutated genes in human cancer.

Table 2
Cancers associated with tumor supressor genes

Gene	Inherited	Somatic	Normal Function
Rb1	Familial retinoblastoma	Retinoblastoma, osteosarcoma, breast and prostate cancer	Transcriptional regulator
Tp53	Li-Fraumeni	50% of all cancers	Transcription factor
Ink4a	Familial melanoma and pancreatic carcinoma	Breast, lung, pancreatic, and bladder cancers	CDK inhibitor
ARF		15% of all cancers	Regulates p53 stability through Mdm2
WT-1	Denys-Drash Syndrome	Wilms tumor	Transcription factor
NF-1	Neurofibromatosis type 1	Neuroblastoma, melanoma	GTPase
BF-2	Neurofibromatosis type 2	Schwannoma, meningioma, and ependymoma	Membrane link to cytoskeleton
APC	FAP, Gardner syndrome, and Turcot syndrome	Colorectal cancer	Regulates β-catenin
VHL	Von Hippel-Lindau syndrome	Renal carcinoma and hemangioblastoma	Regulates HIF-1α
BRCA1	Inherited breast and ovarian cancer	Ovarian and breast cancer	DNA repair protein
BRCA2	Inherited breast and pancreatic cancer	Breast and pancreatic cancer	DNA repair protein
PTCH	Gorlin syndrome and hereditary basal cell carcinoma	Basal cell skin carcinoma and medulloblastoma	Receptor for sonic hedgehog
PTEN	Cowden syndrome	Glioma, breast, and prostate carcinomas and head and neck squamous carcinoma	PI3 phosphatase
E-Cad	Familial gastric cancer	Gastric (diffuse type) and lobular breast carcinoma	Cell-cell adhesion protein
LKB1	Peutz-jeghers syndrome	Colorectal cancer	Ser/Thr protein kinase