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# NEOPLASIA

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→ In Neoplastic cells → Non-Lethal damage to DNA.

→ When mutation in (Proto-Oncho) genes → they are converted into (Oncho) genes → start over proliferating uncontrolably.

→ (Mutation): "Permanent Alteration in DNA w/c is heritable to the next Daughter cell ——."

* Every day there are 10,000 injuries to DNA w/c are repaired → so they aren't mutation.

## For A Cell to Be Neoplastic :

* It should be self Sufficient to Proliferate. (oncho genes → Activated)
* It should be Insensitive to Anti-Proliferative Signals. (Tumor Suppresor genes → Deactivated)
* Its repair System → Not functional - (DNA repair Genes → Not-functional)
* Its Apoptotic System → Not functional - (Pro-Apoptotic Genes → " " )
  (Evasion of Apoptotic System) (Anti-Apoptic Genes → Gain of function)
* Limitless Replicative Capicity - (Telomerase Producing Gene → Gain of function)
* Sustained Angiogenisis -
* Invasion + Metastasis - (Malignant)
* Escape from Immunity.

→ Normally during each replication → Ends of chromosome (Telomeres) shortens → A stage come that Telemers → so much short → No further Replication.

→ Some cells → high Repl - Power/Capicity → → (Telomerase) → More Active.

→ But Cancerous Cells →
→ Telomerase → Over Expressed
→ Keep on adding Nucleotides at Telomeres → cell keep on Proliferating → Replicating.

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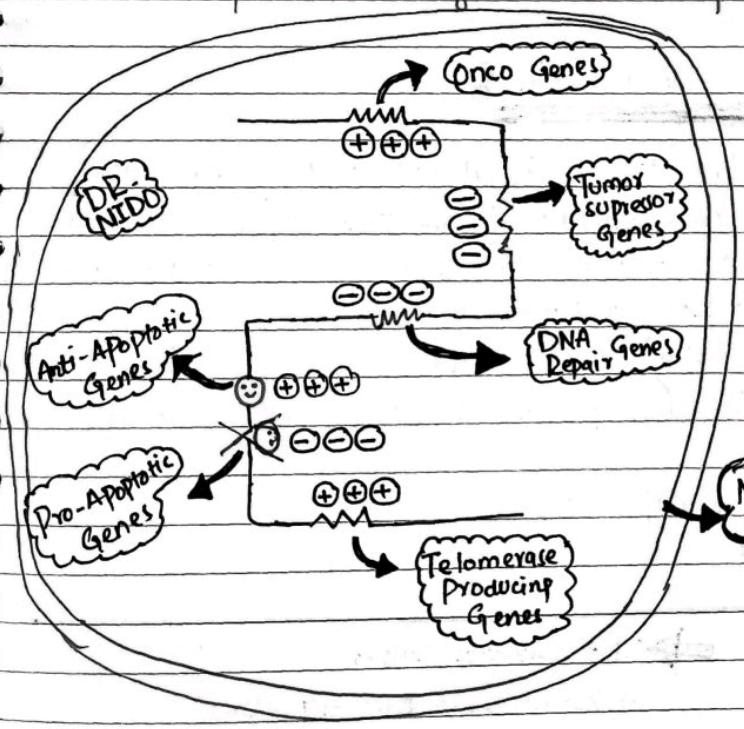
## Metastasis :

→ Normal cells → well Differentiated → can only survive in its own micro Environment → i.e liver cell cannot grow in Brain.

But Malignant cells → so much mutated → that some Embryonic genes → Activated → undifferentied characteristics → → can grow in any tissue micro Environment → → i.e can spread throughout the body & can replicate throughout the body.




- ⊕ → Gain of Function.
- ⊖ → Loss of Function.

# GENETICS OF NORMAL CELL CYCLE

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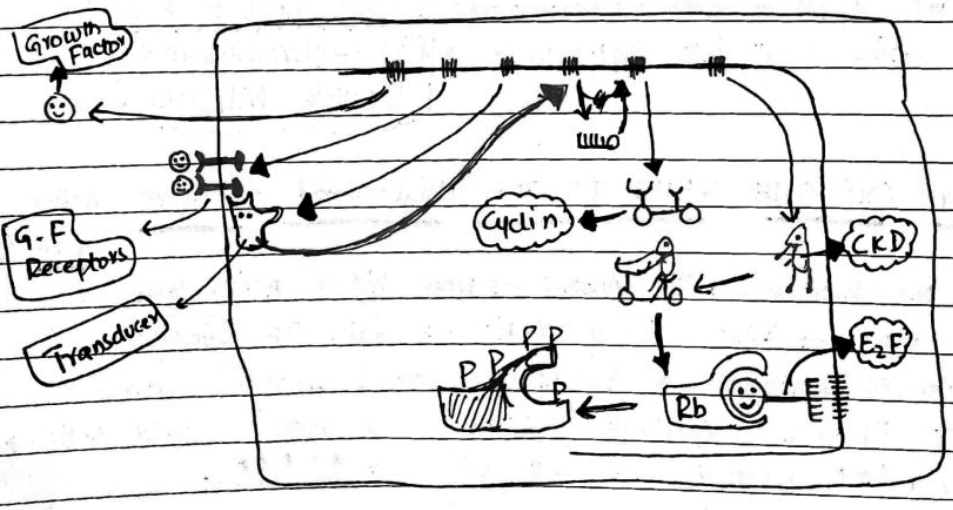
→ When cell is resting / Normal state → It is in (G0-phase).

→ When it is about to proliferate → It is in (G1-phase).

→ In G1-phase → 1st gene → Activated → make protien → (Growth Factor).
→ Then another gene → Activated → another protien → (Growth Factor Receptor).
→ Growth Factor binds wd G-Factor Receptor → Dimerization occurs →
→ Tyrosine Kinase Activity.
→ Then another gene → protien → (Signals Transducers) → All time sticking wd membrane. → signal back to DNA. → Activate another Gene → (Responder Gene) → w/c make protien →
→ w/c act on other gene → activated → produces
→ (CYCLINs) → w/c activate (cyclin-dependant kinases) → (CDK) w/c in turn phosphorylates (Rb-Protien) w/c become inhabited & (E2F-Protien) become free from it → cell synthesis genes →
→ Activated → (S-phase)

* Production of Cyclins → G1 → (S-phase).
* (Rb) → Also called (Retinoblastoma) → b/c first discovered in Retinoblastoma But Actually → they are present in every cell of body.

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# Genetics OF CACEROUS CELL

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## ① GAIN OF FUNCTION (ONCHO-GENE) or Proto Oncho

### ● Point Mutation In Proto Oncho Gene / Chromosome :

→ Due to this gain of function of Genes may occur.

e.g :

* Gene for Growth Factor → gain of function → Growth Fact. → become too much sticky → didn't detach from Receptors → → so Continuous Signals to cell Synthesis.

* Gene for G-F Receptors → gain of function → Dimerization occur even in absence of G. Factors → so Continuos Signls—.

### ● GENE - AMPLIFICATION :

→ During Replication → Many copies of One Gene is made. So Every copy → produce normal proteins → But Total no. of Protien → Too much bz of many copies of Gene → → so Gain of function of that Gene occurs.

** Too Many Copies of Gene → Chromosome → Can't hold it → So some copies → fall into Cytoplasm → (Extra-chromosomal Double Minutes)

### ● SHIFTING OF ONE GENE TO THE Neigbourhood of highly Active Gene :

→ Gene from one chromose → To Another → Near highly Active gene → → so this gene → also highly Active → Gain Of function.

e.g: In Follicular Cell Lymphoma → Anti-Apoptotic Gene (BCl2) → shift from Chromo-18 to 14 → Near Antibody Producing gene w/c is highly Active → → so Bcl-2 → ↑↑↑ Expressed → Cell life → ↑↑↑↑↑.

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⊛ Proto-Oncho Genes → Dominant Genes → If one Allele of Copy → Mutated → Cell over proliferates.

⊛ Tumor Suppresser Genes (Rb etc) → ~~Dominant~~ Recessive Genes.

→ Proto-Oncho → Gain of function → Oncho-Genes.

★ Tumor Supresser → If one copy → Mutated → still the other Allele → Sufficient to prevent cell from over-Proliferation.

## PROTO-ONCHO-GENES

1. Growth Factor Genes :
   → Platelets Derived Growth Factor Gene.
   → Epithelial G-F. Gene. etc.

2. G-F-Receptor Genes :
   → PDGF-R Gene
   → EGF-R Gene etc.

3. TRANSDUCER GENES : (Most Common Mutation In Proto-Oncho- is Mutation of Transducer gene)
   → Ras-Gene

★ Normally Ras has GDP & is inactive → when It is stimulated → It looses GDP & Acquire GTP & Give Signal to Nucleus through Raf-Map etc pathway.
But once it give signal → It has Intrinsic GTPase activity w/c Breaks its GTP to GDP again & become inactivated.
→ Also Tumor Suppresor Gene produce protien w/c Stimulate it GTPase activity.

(P-T-O)

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* Now Ras is Mutated → when become active → GTPase activity is lost → so given signal again & again.

→ Also some times Tumor supressor → Mutated → cannot stimulate GTPase activity → so again → signal → again & again.

(4) Transducer Gene :

* ABL-Gene / Tyrosine kinase → usually inhabited by Tumor supressor.

But in Chronic Myloid Leukemia (CML) → ABL gene → translocated from Gene-22 to Gene-9 near BCR-gene.

bcr & ABL → fuses → make Hybrid gene → Hybrid protien → w/c is not inhabited by Tumor Suppressor → so cell keep on proliferating.

● IMATINIB MESYLATE Drug → selectively inhabit mutant-ABL → & also this drug has least side Effects.

* myc, cyclin genes etc → same gain of function → → over proliferation of cell.

→ Cyclins → Not all the times present → One type of cyclin produced when cell cycle move from one phase to another. Then Another type of cyclins → produced → cell cycle → Another phase

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## (2.) TUMOR SUPPRESSOR GENES (LOSS OF FUNCTION)

→ Actually These genes stops over proliferation of cells when cell is normally Proliferating → But their absence → cell over proliferation → Tumor.

★ Rb-Gene → Present in all cells. → Physiological Brake.

* Retinoblastoma - Gene

* Rb-protein → Present in all the cells w/c is not Proliferating.

### Retino Blastoma

**Sporadic**

→ 60 %
→ Old Age
→ Unilateral
→ Both Alleles → normal → mutation → in one then in another → so will occur in old age.
→ Cannot Pass it to offsprings.

**Heriditory**

→ 40 %
→ Young Age
→ Bilateral
→ defected Allele from Parents & mutation in 2nd Allele → → chances → more → Young age.
→ can Pass defective Allele to offspring.

* For Retinoblastoma to develop → both Allele should be disfunctional.

→ On chromosome ~~11~~ (13) → Rb.

**Knudson 2-HIT HYPOTHESIS :**

→ "To develop Retinoblastoma → Both the Alleles of Rb-gene must be hit by mutation ——."

→ Later on this hypothesis → True in All Tumor suppressor genes.

→ Those People who have one mutated Rb-gene/Allele → Also have risk of developing Osteo Sarcoma & some other tumors as well.

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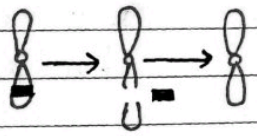
## HOW LOSS OF FUNCTION MUTATION OCCURS :

① Interstitial Deletion :
→ " A piece of chromose / gene → deleted & remaing chromosome fused again ——."



② Missing Chromosome :
→ whole chromosome is missing ——.

③ Point Mutation :
→ Point mutation occur in gene → produce products → w/c cannot Perform its normal function.

⇒ Loss of Function → Must be in Both Alleles.

★ **Rb-gene** → Recessive
★ But Heridatory Retinoblastoma → inherited in Autosomal Dominant Fashion?
→ This is bcz Patient has already inherited one Mutated Allele through Germ line & need Just one Hit from Envirounment.
→ Although gene → Recessive bcz Retinoblastoma only develops when both Alleles are defective.
→ But the Carriers (one defected Allele) → is so much valnurable to Envirounmental Hit. → easily get defective.

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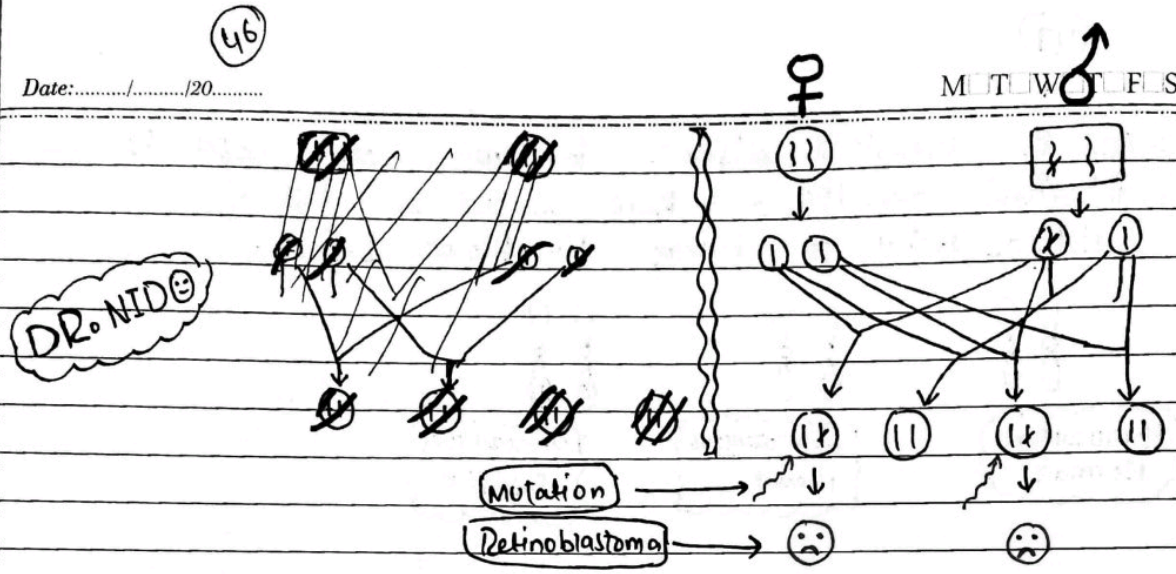


● All the Growth Factors → Stimulatory Except Transforming Growth FACTOR-β (TGF-β) → inhabitory.
→ Normally TGF-β-Gene produces TGF-β. & other gene produces TGF-β-Receptor.
→ TGF-β binds wd TGF-β ® → w/c will stimulate CDK-Inhabitor gene → w/c produces (CDK-inhabitor).
→ CDK-I → inhabits CDK-cyclin complex → thus phosphorylation of Rb-protien → inhabited → cell over-proliferation → inhabited.

☆ So In (Neoplasia) → TGF-β gene → Both Alleles → Mutated → → loss of function.

## Also Normally → After cell cycle → Phosphatases → remove phosphates from rb-protien & it became Active again.

● HUMAN PAPILOMA VIRUS (HPV) → increases → risk of (Cancer. Cervical)
→ HPV-16 → produces protien → (E-7) → These protiens gets attached to rb-gene → so rb cannot hold $E_2$-F → so cell cycle → continues → over proliferation → Cervical Cancer.

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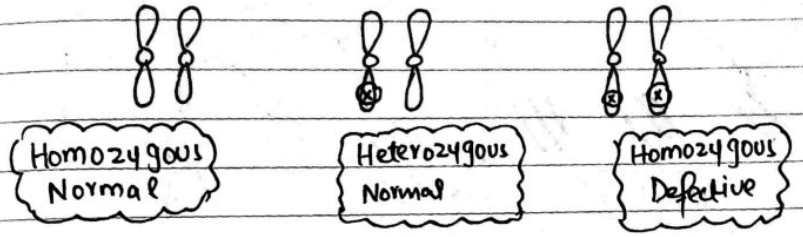
- All the inherited diseases in w/c one copy is inherited defective → there should be loss of Heterozygocity to develop Full-Blown Defect.




- **P53** (Important Tumor Supressor Gene) :: (Guardian of Genome) ::

→ Not Active all the time but become activated when there is some Serious damage to DNA.

→ When DNA is synthesizing normally → If any abnormality occurs → ATM-gene (DNA Proofreader gene) → signals P53 w/c become Activated → make product → w/c activate another gene → w/c make CDK-Inhabitor → thus cell cycle is stopped Immediately. (P-16)

→ P53 also Activates DNA-repair gene w/c make Prdiens/Enzyme → repair the Abnormality in DNA.

→ when repair → done → No more signals from Proofreaders to P53 → so P53 switched off.

(P-T-O)

* A → Ataxia
* T → Telangiectasia
* M → Mutated

→ First discovered in this condition (or) ATM → Mutated in this condition.

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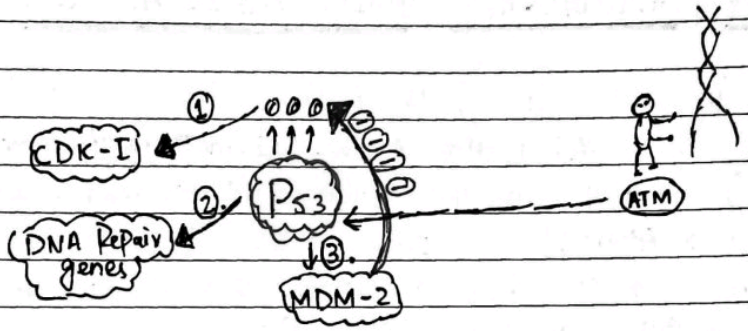
→ But Before switching off → P53 Activates another gene (MDM-2) w/c destroy P53-proteins → so CDK-I → ↓↓↓ → cell cycle → Continues again.




→ IF DNA → Severly damaged → that (P53) cannot repair it by activating DNA repair genes → then P53 directs the cell to Apoptosis so that this damaged DNA cannot Pass to next generation.

→ So P53 → Pro-Apoptotic genes → BAX → neutrilize effect of Bcl-2 on Mitochondrial channels → cyt-C → come out → → Activates Caspases → Apoptosis.

● In (Cancer) → Both Alleles of P53 → Mutated + loss of function.

★ P53 → on chromosome # (17)

→ Most Common Proto Oncho / Dominant gene affected in Cancer → (Ras)

→ " " Tumor Supr- / Recessive " " " " → (P53)

★ Li-Fraumani Syndrome

→ One Copy of P53 → inherited thru germ line.

→ 25% of more chances to develop multiple type of Cancer at age of 50 yrs.

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- HPV ⇒ Produces E-6 → Binds wd P53 → Stops it function.

## → WHY SOME CANCERS ARE RESPONSIVE TO CHEMOTHERAPY / RADIOTHERAPY WHILE OTHERS ARE NOT ?

★ Those cancers in w/c P53 is Active are responsive bc2 when we use Alkylating Agents (Chemotherapy) or Radiations (Radio-) → they damage DNA → Proofreader genes signals P53 → Attempt to repair → But Damage to DNA → severe → so P53 → Directs → cell to → → Apoptosis → thus Cancer → Responsive.

★ Those cancers → P53 → In Active → Not-Responsive → → No P53 → No Apoptosis.

## ● β-Catenin & APC System ⇒

→ Normally β-Catenin binds wd ~~receptor~~ Trancriptional Factor of MYC-gene w/c in turn activate MYC → Trancriptional factors → cyclin-gene → cyclins → cell cycle → Move forward.

→ APC-gene → Produce products → w/c destroy β-Catenin → → then β-Cat- can't stimulate Proto-Oncho → cell → → over proliferation → stops.

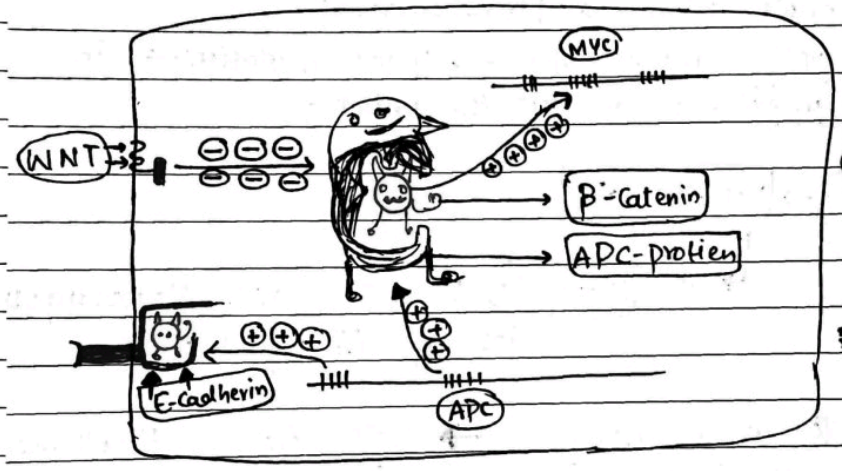
→ WNT → stimulate its receptors → w/c in turn → → destroy APC-protiens → thus β-Cat- → free → cycle → ↑↑↑.

★ So WNT & β-Catenin Sym → Stimulatory to cell cycle.

→ Another gene produces (E-cadherens) → w/c are present on cell membrane → hold β-catenin wd itself & didn't allow it to stimulate Proto Oncho genes.

- E-cadherens also help the two cells to bind wd each other → cell → inhabited → (contact Inhabition).

★ APC + E-Cadherins → Tumor Supressors.




* A → Adenomatous
* P → Polyposis
* C → Coli

* Actually APC-system inhabits Proto-Oncho genes system.

## IN CANCER :

- Loss OF E-CADHERINS :

→ Both Alleles → loss of function.

→ Commonly Seen in Gastric Carcinoma + Esophageal Carcinoma.

→ Also E-Cadherins → lost → cell to cell Contact → lost → → cancerous cell → detaches from Primary mass → Metastasis will also occur.

E-cadherin → ↓↓↓

① * Cells → over proliferate

② * Metastasis

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## Problem wd APC-genes

→ Those who have inherited one copy of mutated APC → → more chances → other Allele → Mutated → At the age → of 20yrs → Thousand Adenomas → Polyps → in their colon.
→ This condition → (Heriditory Polyposis Coli).

★ Treatment:
→ Removal of whole colon → Pan-colectomy
→ bcz if you don't remove colon → Many mutations → in Adenomas → (Cancer) → can kill the patient.

★ In (Colo-Rectal Carcinomas) → [Non-Heridary]
↳ still (70-80 %) patients have Homozygous loss of APC-gene.

→ For a cell to work normally → Both APC & E-cadherins are required i.e Half of β-catenin is controlled by APC & half of β-catenin → by E-cadherins.
So if any of these (2) → lost → cell → over proliferate → → cz → Cannot be controlled by one Alone.

★ Also when β-catenin is (mutant) & both APC & E-cadherin are present → still there will be no effect of these (2) on this mutant β-Catenin & cell will over proliferate.

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## ★ NF-1 (Neuro Fibromin-1) Gene :

→ (Normally) NF-1 increases GTPase activity of Ras-Protien thus preventing the cell from over proliferation by inhabiting proto-Ocho genes.

→ But In (Cancer) NF-1 → loss of Function → Ras → GTPase-activity → down → signaling proto oncho genes → cell → over proliferating.

★ NF-1 → Also Called GTPase Activating Protien (GAP).

## ● NeuroFibromatosis Type-1 : (Von-Recklinghausen Disease)

→ When Someone inherits one defected copy of (gene NF-1) & then there is strong chances of defect in other copy → → defected → Patient develops hundered of Adenomas all over his body w/c may later develop into cancers.

* NF-1 gene → On Chromosome #17.
* Also in Von-Recklinghausen → (17) Alphabets.

## ★ NF-2 Gene :

→ (Normally) NF-2 produces Merlin-protien w/c on one side binds wd CD-44 & on other side binds wd Actin.

→ CD.44 → helps the cell to keep stabilized relationship wd Extracellular matrix & neighbouring cells.

→ So CD-44 + Merlin + Actin → Contact inhabition.

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→ In (Malignancy) → NF-2 → defective / loss of function → no Merlin → → no Contact inhabition → Cells over proliferate.

## ★ Neuro Fibromatosis - II :

● Patients → develops → (Schwanomas) → Bilateral → on 8th Cranial Nerve / VestibuloCochlear Nerve.

→ One Copy → inherited. → 2nd → easily mutated.

→ These patients also have risk of developing other Tumors / Meningiomas of CNS.

## ★ Von Hipple Lindau Gene :

→ Normally when there is Hypoxia in body → It stimulates a gene w/c produces Hypoxia Inducible Factor (HIF).

→ HIF stimulates (2) genes Vascular Endoth. Growth Factor (VEGF) & platelets derived Growth Factor (PDGF) → w/c causes Blood vessels formation → So that Blood Supply to that Ischemic part is increased.

→ But After Production → HIF needs to be destroyed →

→ w/c is done by Ubiquitin.

★ (Ubiquitin - Ligase) → causes ligation / binding b/w HIF & Ubiquitin.

→ This Ub-ligase is Produced by "Von Hipple Lindau gene".

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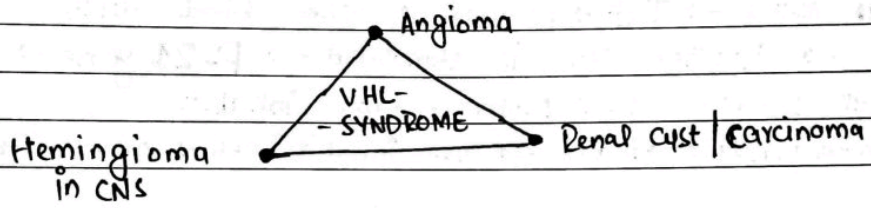
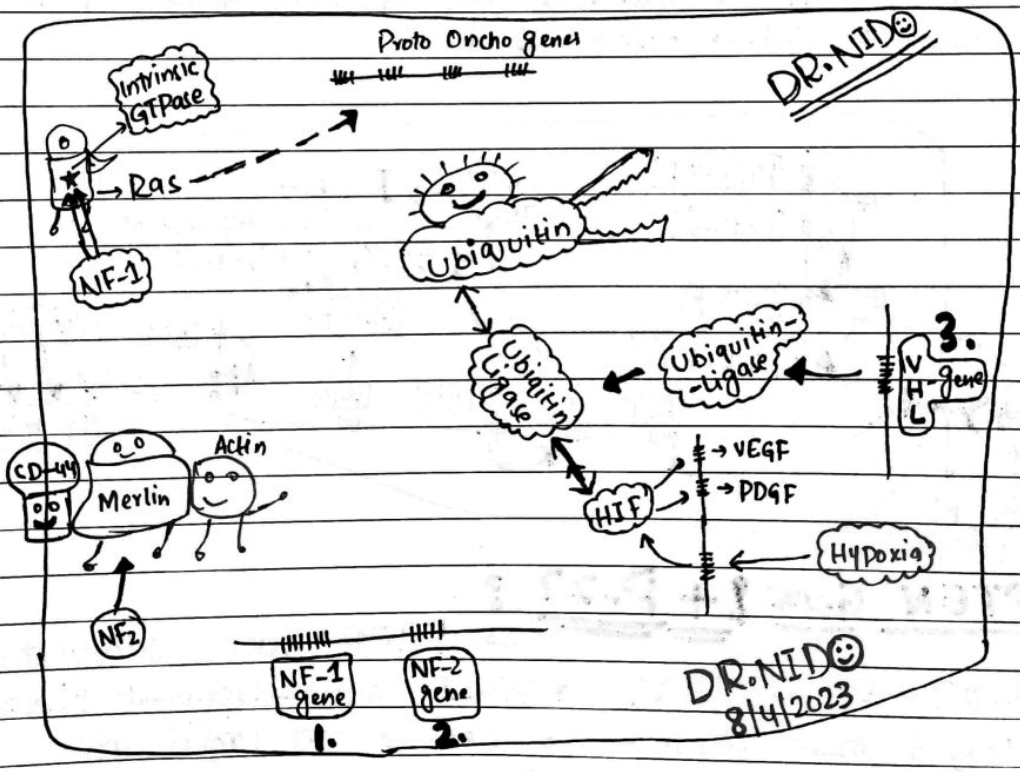
# VON HIPPLE LINDAU SYNDROME :

→ VHL-gene → defective → Patients → develops (Vascular Tumors) in the body.

★ Patients develops → Angioma in Retina + Hemingioma in the cerebellum + Renal cysts / Renal cell carcinoma.



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## ★ TGF-β Gene :

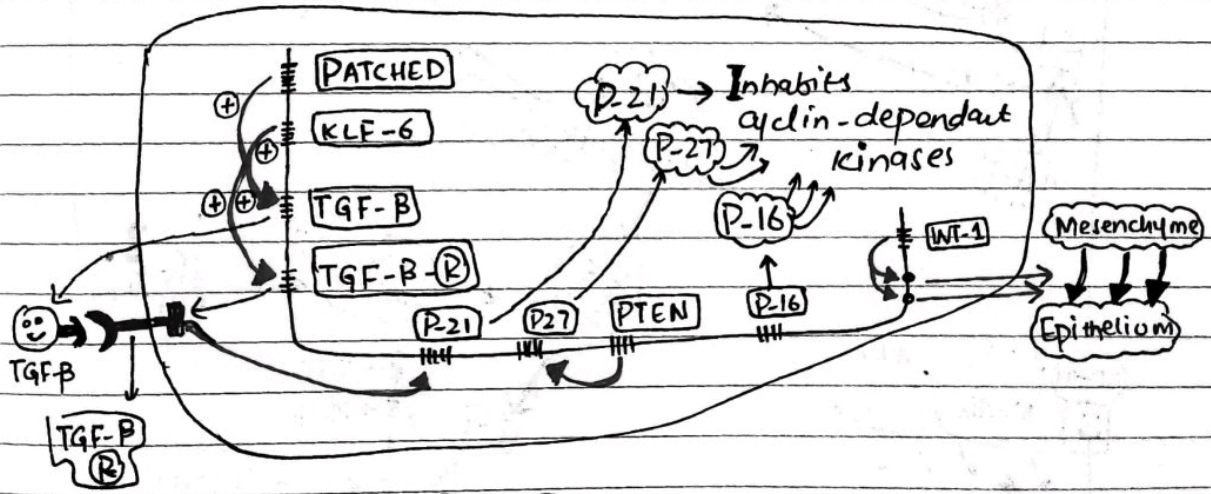
→ TGF-β gene produces TGF-Protien.

→ & TGF-β Receptor gene → produces TGF-β-Ⓡ for TGF-β protien.

→ Genes called PATCHED Gene & KLF-6 → Both have stimulatory effect on TGF-β & TGF-β-Ⓡ genes.

→ Thus PATCHED & KLF → stimulate TGF-β & TGF-β Ⓡ genes → → as a result → TGF → produced → when binds with TGF-Ⓡ → Another gene is stimulated → P-21 gene → w/c will produce P-21 protien → w/c inhabits cyclin-dependant kinases → thus inhabit cell → over proliferation.

★ Any loss in both Alleles of any of these Genes → P-21 → lost → Cell → over proliferate.




## ★ PTEN Gene & P-27 :

→ P-TEN gene stimulates P-27 → & P-27 → inhabit cyclin-dependant kinases.

* Loss in these Genes → Cell → over proliferate.

★ P-16 → same like P-21, P-27.

| Sr. No. | Date | Topic |
|---|---|---|
| | ★ | **Wilm's Tumor-1 (WT-1) Gene :** |
| | | Willim's Tumors :<br>→ Most Comon Renal Tumors of children :-<br>→ Some times → so massive → whole Abdomen → Protruberant. |
| → | Normally | WT-1 gene stimulates ② genes → w/c in turn produces Differentiation Factors → w/c Differentiate Mesodermal cells into Epithelial cells in Kidneys. (Mesenchymal) |
| → | Loss in | WT-1 → no Epithelial differentiation → Tumor develops in Kidney w/c may contain bone, cartilage, Muscle etc (Derivatives of mesoderm/ Mesenchyme) →<br>→ Willim's Tumor. |

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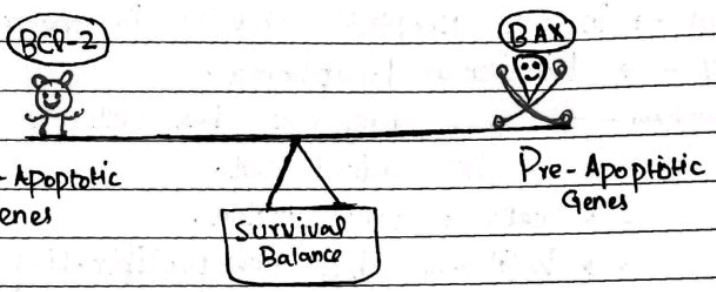
## (3). Cancerous cells → Anti-Apoptotic ⁰₀ (Evasion OF APOTOSIS)




* In Normal cell → there is balance b/w Pro-Apoptic & Anti-Apopt-
→ If Pro-Apoptotic → ↑↑↑ → cell → Apoptosis → Dies.
→ " Anti- " → " → " → survives -

* But In Neoplasia → Anti-Apoptotic → ↑↑↑ & Pro-Apoptotic → ↓↓↓ →
→ cell → survives → for long time.

☆ BCl-2 → Gain of function
☆ BAX → Loss of function
→ Neoplasia

### ★ Gain OF Function OF Anti-Apoptotic Genes ⁰₀

* Normally → Bcl-2 → inhabs the exit of cyct-c from mitochondria & thus preventing → Activation of Caspases → inhabiting → Apoptosis.

### ★ B-Cell Lymphoma (Follicular Type) ⁰₀ (18-14 Translocation)

(translocated)

→ BCl gene on chromosome # 18 → shifted to chromosome # 14 near highly active Immunoglobulin (Ig-Gene). Thus BCl → also become highly active → BCl-2 ↑↑↑ → Apoptosis → ↓↓↓ → cell → live longer. cell → living longer → Chances of mutation → ↑↑↑ → Also Resisting → → Apoptosis → Neoplasia.

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→ Normally mature B-Lymphocytes → (Tendancy) make follicles in Lymph Node.

→ So Lymphoma → in w/c Neoplastic changes in Mature/well differen-tiated B-Lymphocytes → Follicular Lymphoma.

→ Follicular Lymphom → less danperous bc2 cells → some what like adult cells.

→ " → cells → over survive.

→ " → Relatively less over proliferating.

→ Indolent Lymphoma.

**Diffused Lymphoma | Burkitt Lymphoma : (8→14 Translocation)**

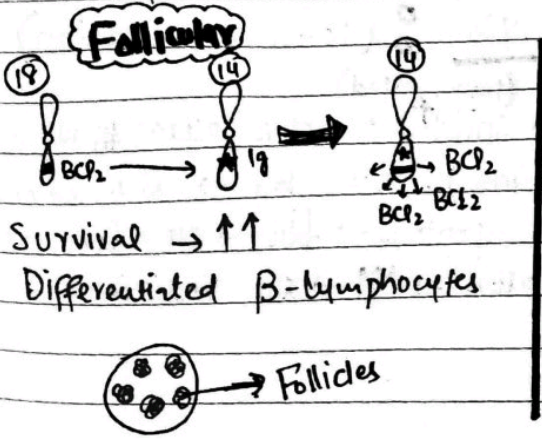
→ On chromosome # 8 → myc-gene → mutated → over proliferating → shifted to chromosome # 14 → B-cells → over proliferate → → but less/not-differentiated → no follicles.

→ Danperous → bc2 → Rapidly proliferating.

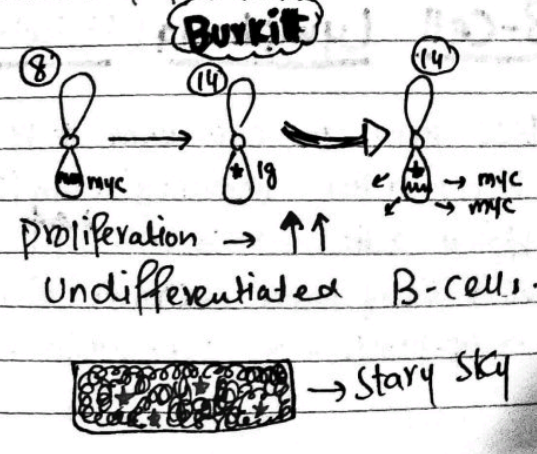
→ Aggressive Lymphoma.

● Some times Follicular Lymphoma may get Converted into Diffused Lymphoma.

→ Histologically → sheets of B-Lymphocytes in b/w w/c star like Necrotic cell/Macrophages are present → Stary-Sky Appearance w/c is seen in Burkitt's Lymphoma.




* Survival → ↑↑
* Differentiated B-Lymphocytes
* → Follides




* Proliferation → ↑↑
* Undifferentiated B-cells.
* → Stary Sky

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* 18 → 14 → 18 yrs. old boy → 14 yrs old girl → → Mature → well differentiated → Follicles | Follicular Lymphoma.

* 8 → 14 → 8 yrs old boy → 14 yrs old girl → Immature → or Girl is like his mother → & Mothers are (برکت) Barkat for children → Burkitt's Lymphoma.

## ★ Loss of Pro-Apoptotic Genes :

→ Either → BAX → loss of function.
→ or → P53 → loss of function. (bcz P53 stimulates BAX)
→ or → MDM-2 → Gain of function. (bcz MDM-2 inhabits P53)

* In All such situations → Apoptosis → inhabited & cell will survive more.

X X X

## ④. DNA Repair Mechanism

→ Every day → DNA encounter 5000 - 10,000 injuries / damages & most of them → repaired for survival of organism.

→ Failure of DNA repair sym → doesn't directly prodoces Neoplasia but it play a vital role in it by allowing alot of mutation in proto Oncho genes, Tumor supressor genes etc.

→ Some People → born wd heridatory defect in DNA repair Mechanism → → high risk of developing Neoplasia → These People → Suffering from → "Genomic Instability Syndrome".

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## (1). DNA Mismatch Repair System :

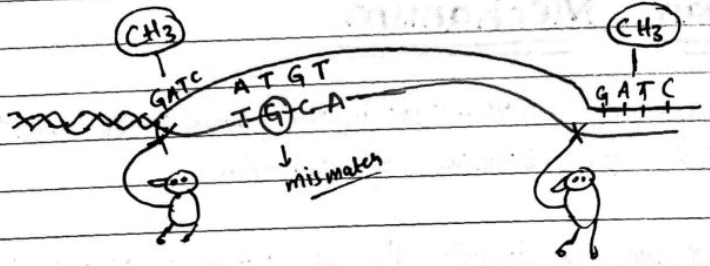
→ Normally Newly synthesized DNA is double checked i.e while synthesis → Polymerases first read parental Nucleotides sequence then add complimentary base pairs.

→ 2ndly when DNA is synthesized → it is wholy scanned again → proofreader → read both strands & find mismatch.

How Enzymes know which strand is Parental & wic is Newly Synthesized ?

→ Actually Parental DNA → at G.A.T.C region is Methylated & newly formed DNA → no methylation.

* So when Proofreaders finds mismatch they makes cuts at methylated points in Daughter DNA & then another polymerases remove bases one by one & insert correct bases & finally ligation occurs at cuts points.




## Heridatory Non-Poly Posis Colon Carcinoma : (HNPCC)

→ DNA mismatched sym → defected → bcz one allele → defected heridatorily & other → thru Environmental etc.

→ so chances of mutation → move & not repaired.

(P-T-O)

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→ Most commonly affects cecum & Proximal colon.
→ Runs in families.
→ Usually MSH-2 gene → defective.
→ In females → there is also increased risk of Endometrial & ovarian carcinoma as well.

● **Tandem Repeats / Micro satellites :**
→ A sequence of 2-6 Nucleotides in DNA w/c are repeated again & again.
→ They remain same for one individual i.e everyone have same Paternal & maternal micro satellites in their each cell.
→ Vary from person to person.
→ Used for identification of individual → DNA Finger printing.

→ To keep the micro satellites in place generation after generation → DNA repair system should be Normal.
→ If DNA repair sys → mismatched → micro satelites → not in correct position / Inbalanced → so in patient wd (HNPCC) will have different microsatelites in colon than rest of body.

● **Replicative Error Phenotype :**
→ "change / variability in micro satellite from cell to cell or tissue to tissue within the same individual ——— ."

→ Those People who have familial / Heridatory colon carcinoma will develop carcinoma at younger age usually while those who have Sporadic type → develop it at Older age bcz in familial → One Gene → defective already through Germ line.

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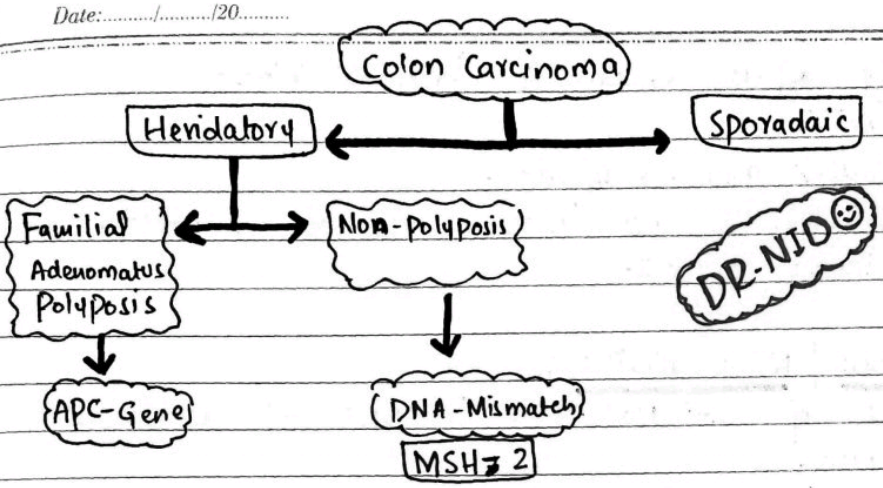


## ②. Nucleotide Excision Repair (NER) :

→ Causes a disease → Xeroderma Pigmentosa.

→ This system involves when damage to DNA is more severe.

→ Caused by Ultra voilet light classically. (* UV-B (280-320 nm))

→ UV causes cross linking b/w pyramidines esp. Thymine → T-T dimers are formed.

→ Normally when dimers are formed → Same ultra voilet activates another enzyme UV-specific EndoNuclease w/c will repair it in the following sequence.

* It will Recognize it first & then will make nichs/cuts at 5' & 3' ends of dimer → EndoNuclease Activity.
* Then this Segment is Removed & New bases are added → Polymerase.
* Then ends are ligated.

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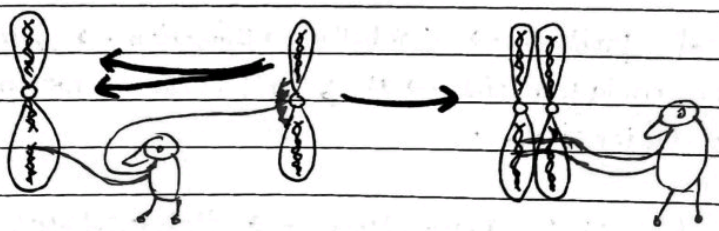
→ In Xeroderma Pigmentosa → one Allele of UV-specific Endonuclease enzyme is defective → DNA repair → not working properly & wd time → other Allele also defective → so Repair mechanisms → → stops → Mutations accomolates in skin cells → Carcinogenisis.
→ Risk of developing skin Carcinomas → 1000 times more than normal.
→ Chances → more in white People of European origin → → setteled near Equator → even if Genes normal → still sunlight → too much → Can cause the System to be overwhelmed.

## ③. Homologous Recombination Repair :

→ When there is very much severe damage to DNA ie. both the strands are broken down then this repair system come into action.
→ When the enzymes find broken pieces → they bring Homologous chromosome to that defected chromosome & then repair it accordingly.

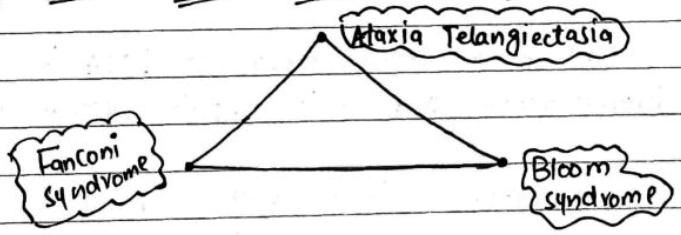


* On (2) occations → Homologous chromosome come near to each other → (1). during meosis (2). During sever DNA damge repair.
* Alkylating agents & Radiation → Causes sever damage.

* Following genes are required to repair Double strand repair:
  ①. Ataxia Telangiectasia gene/Protien
  ②. ~~BRCA1 BRCA2~~ BRCA-1 gene/Protien
  ③. BRCA-2 gene/Protien
  ④. RAD-51 protien
  ⑤. Fanconi Anemia Protien Complex.

→ First A-T protien & F.A-P-complex (Double stranded DNA repair Sensors) will locate the damage then they will phosphorylate BRCA-1 & ② w/c along wd RAD-51 → will repair the defect.

→ If these Repair System is dificient:




● ATAXIA TELANGIECTASIA ∴ (By Ionizing Radiation)

* Neurological problems → Cerebellar dysfunction → Purkinji cell → damaged.
* Lymphoid melagnancies → as B & T-cells → not matured properly.
* Immuno difiencient.

→ (1%) of U-S population → Heterozygous for this gene → so high risk of developing melagnancies even by slight radiation.

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## Bloom Syndrome : (By Ionizating Radiation)

* Rare → multiple developmental + Conginital defects.
* Tendancies to develop cancers due to Impaired DNA repair system.

## FANCONI ANEMIA : (By Alkylating Agents)

* Anemia → bc2 → Hematopiotic cells → defective.
* Impaired Double Stranded DNA repair.

## BRCA-1 & BRCA-2 Gene Defects :

→ When one copy of Defective BRCA-1 & or BRCA-2 →
→ there is high risk of developing Breast Cancers.

**BRCA-1 only :**

→ Females → Affected
* Breast Carciuoma
* Ovarian Cancer

**BRCA-2 only :**

→ Both Male + Female
* Breast cancer in both Male + Female.

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## ⑤. Limitless Replicative Capicity Of Cancerous Cells:

→ Normal cells → limited replicative capicity → bcz ends of chromosome (Telomeres) → shortens after every replication → → when significantly shortened → P53 → activated → BAX-gene → → Apoptosis → cell dies.

→ But In cancer cells → an enzyme (Telomerase) keep on elangating the telomeres → so cancer cell → limitless replicative capicity.

- Physiologically → high telomerase activity → In stem cells.
  * Also in Gemetes → zygote → high telomerase → so too much replication → untill make Complete Human being.

* Sometimes Telomerase → not defective but (P53) → defective → → so chromosome shortning → signal P53 but P53 is not there to start Apoptosis → so cell → keep on proliferating & shortning chromosome → danperous mutations.