Normal Function of TP53 (Tumor Protein 53)

TP53 is a **tumor suppressor gene**, meaning it helps prevent uncontrolled cell growth (i.e., cancer).

🧠 Key Functions of Normal p53 Protein (product of TP53):

- **DNA Guardian**: Monitors DNA integrity — nicknamed the **"Guardian of the Genome"**.
- **Stress Sensor**: When DNA is damaged (by radiation, chemicals, etc.), p53 levels rise.
- **Transcription Factor**: p53 binds to DNA and activates transcription of genes that:
  - ☠️ Trigger apoptosis (cell death)
  - 🛠️ Induce DNA repair
  - ⏸️ Arrest the cell cycle to prevent replication of damaged DNA

🔑 Example Pathway: p53 → CDKN1A (p21) → p21 blocks CDK → prevents phosphorylation of Rb protein → cell cycle is halted in G1 phase.

Mnemonic: "p53 protects by Pausing, Programming repair, and Prompting death."

🧬 TP53 Mutations and Their Consequences

Mutations in TP53 are found in **over 50%** of major cancers like:

- Colorectal
- Breast
- Lung cancers

🧱 Mutation Site:

- Most mutations affect the **DNA-binding domain** of p53 → prevents it from activating repair or apoptosis genes.

❌ Key Outcomes of Mutation:

1. **Loss of Function**: Damaged cells continue dividing instead of undergoing repair or apoptosis.

2. **Dominant Negative Effect**: Mutant p53 protein interferes with the normal p53 from the other allele → this **violates the two-hit model** (usually both alleles must be hit, but here, one mutant copy dominates).
3. **Cancer Formation**: These faulty cells accumulate mutations and become tumors.

🦠 Viruses & TP53

Some viruses **inactivate p53**, aiding cancer development:

- Example: **HPV (Human Papilloma Virus)** causes **cervical cancer** by:
    - Inactivating both **p53** and **pRb** → allows uncontrolled growth.

☠️ Carcinogens & TP53 Mutations

Mutations in TP53 can be **traced to specific carcinogens**:

- **Aflatoxin B1** (in moldy grains) → Arginine → Serine substitution in p53 (liver cancer).
- **Benzopyrene** (in cigarettes) → TP53 base pair changes in lung cancer.

Mnemonic: "AFlaToxin hits the Liver, Benzo hits the Lung."

Analyzing TP53 mutations in a tumor can help **identify the carcinogen** responsible for that cancer.

🧬 Li-Fraumeni Syndrome (LFS) – Inherited TP53 Mutation

- A **genetic syndrome** caused by **germline TP53 mutations** (passed from parents).
- **Autosomal Dominant**: Only one mutant copy is enough.
- **Cancers Involved**: Breast, colon, brain, soft tissue, bone, leukemia, adrenocortical.
- **Early Onset**: Cancer often occurs **young** and **in multiple organs**.

🧮 Risk:

- 50% develop invasive cancer by age **30**

- Over 90% by age **70**

Other Cause: CHEK2 Mutation

- CHEK2 phosphorylates p53 in response to radiation → activates it.
- Loss of CHEK2 → p53 not activated → similar cancer risk.

Mnemonic: "CHEK2 checks the p53 switch."

🧪 Clinical Relevance of TP53 Mutations

- **Poor Prognosis**: TP53 mutations are found in **aggressive tumors**.
- **Prognostic Marker**: Presence indicates worse outcomes.
- **Gene Therapy Research**: Scientists are trying to insert **normal TP53** into cancer cells → hoping to trigger **apoptosis** and shrink tumors.

APC

🧬 Normal Function of the APC Gene

APC (Adenomatous Polyposis Coli) is a **tumor suppressor gene** found on **chromosome 5q**. Its main role is to **regulate cell growth**, prevent **uncontrolled proliferation**, and **maintain genome stability**.

🔑 Normal APC Protein Functions:

1. **Wnt Pathway Regulation**:
    - APC controls the **degradation of β-catenin**, a protein involved in the **Wnt signaling pathway**.
    - **Without Wnt signals**, APC forms a destruction complex that **phosphorylates β-catenin**, marking it for degradation.
    - This **keeps β-catenin levels low**, preventing the activation of genes like **Myc** that promote cell proliferation.
2. **Cell Adhesion Regulation**:
    - APC helps anchor **β-catenin to E-cadherin** at the cell membrane, maintaining **tight cell-cell adhesion**.
    - This helps **prevent invasion and metastasis**.
3. **Chromosome Stability**:
    - APC plays a role in **microtubule binding** during mitosis.

- Ensures proper **chromosome segregation** and prevents **aneuploidy** or chromosome breaks.

Mnemonic for APC Roles: "**A**ttaches cells (adhesion), **P**revents proliferation (Wnt/β-catenin), **C**ontrols chromosomes (genomic stability)."

❌ What Happens When APC Is Mutated?

🧠 General Consequences:

- APC mutation → β-catenin not degraded → builds up in the nucleus → activates **pro-growth genes** like **Myc** → uncontrolled cell division.

🧬 In Familial Adenomatous Polyposis (FAP):

- **FAP is an autosomal dominant disorder** where one mutated APC allele is inherited (**first hit**).
- The **second allele is somatically mutated** later in life (**second hit**, follows the **two-hit model**).
- This leads to **hundreds to thousands of colonic adenomas** developing by the second or third decade of life.
- If untreated, nearly all patients develop **colorectal cancer** by middle age.

Mnemonic: *"FAP = Full of Adenomatous Polyps."*

🔬 Additional Details & Links to Other Concepts

🔍 APC Mutation in Sporadic CRC:

- Even people without FAP often acquire **somatic APC mutations**.
- These mutations are often **the first step** in the adenoma-carcinoma sequence but aren't enough **alone** for cancer — additional mutations are needed.

🧩 Key Genetic Events in CRC Progression:

1. **APC loss** → adenoma formation
2. **KRAS activation** → increased proliferation
3. **TP53 loss** → decreased apoptosis, more mutation accumulation
4. **SMAD4 loss** → disrupts TGF-β pathway (normally suppresses tumors)

Mnemonic for CRC progression: "**A**PC → **K**RAS → **P**53 → **S**MAD4"
(*"AKPS" – like steps on the staircase of colon cancer*.)

📌 Other Inactivation Mechanisms

Even without mutation, **tumor suppressor genes like APC** can be inactivated by:

- **Promoter hypermethylation** (epigenetic silencing)

This is also seen in:

- **RB1** (retinoblastoma)
- **BRCA1** (breast/ovarian)
- **MLH1** (HNPCC)
- **CDKN2A** (melanoma)
- **VHL** (von Hippel-Lindau disease)

📉 APC Loss Consequences in Detail

Function of APC	Effect of Mutation
🧬 Degrades β-catenin	β-catenin accumulates → activates Myc → ↑ cell proliferation
🧲 Anchors β-catenin to E-cadherin	Weak cell adhesion → ↑ invasion and metastasis
🧷 Binds microtubules in mitosis	Chromosomal instability → aneuploidy, chromosomal breaks → cancer

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👨‍👩‍👧‍👦 Genetics and Inheritance

- **FAP is inherited in an autosomal dominant pattern**.
- **2–5% of all colorectal cancers** are inherited.
- Risk increases if:
  - 1 first-degree relative has CRC → **2–3x increased risk**
  - 2 relatives → **3–6x increased risk**

🧪 Clinical Implications

- **Early detection of APC mutations** via **genetic testing** allows early colonoscopies and prophylactic colectomy.
- **Managing FAP** reduces colorectal cancer risk drastically.
- **APC gene analysis** helps in:
    - Diagnosis of FAP
    - Risk counseling for family members

Hereditary nonpolyposis colon cancer gene (HNPCC)

🧬 Normal Function of HNPCC Genes

✅ Key Genes Involved:

- **MSH2** (most common)
- **MLH1**
- Others: **MSH6**, **PMS2**, and **EPCAM** (affects MSH2 expression)

These genes are involved in the **DNA Mismatch Repair (MMR) System**.

🔧 What Does the MMR System Do?

Every time a cell divides and DNA is replicated, errors (mismatches) can occur — e.g., inserting the wrong base.

🛠 The **MMR system**:

1. **Recognizes mismatched bases** in newly replicated DNA.
2. **Removes the incorrect segment**.
3. **Replaces it with the correct DNA sequence**.

🧷 Gene Functions (Mnemonic: *"My Little Sister Helps Prevent Mistakes"*)

Gene	Role
MSH2	Detects mismatches (pairs with MSH6)
MLH1	Coordinates repair (pairs with PMS2)
MSH6/PMS2	Form heterodimers to help MSH2 & MLH1 function
EPCAM	Mutation silences MSH2 gene via methylation

❌ What Happens When These Genes Are Mutated?

- If **both alleles** (copies) of a mismatch repair gene are inactivated (e.g., by mutation or methylation), the repair system fails.
- This leads to **accumulation of mutations throughout the genome**, especially in short, repetitive DNA sequences called **microsatellites**.

📌 Result: Microsatellite Instability (MSI)

- MSI is a **hallmark** of Lynch Syndrome–associated cancers.
- MSI can also appear in **sporadic cancers**, often due to **MLH1 promoter hypermethylation** (epigenetic silencing), not germline mutations.

🧬 Lynch Syndrome / HNPCC – Summary

📌 Inheritance:

- **Autosomal dominant** (only 1 mutated copy needed to increase cancer risk)
- **Second allele** is typically inactivated somatically

📉 Cancer Risk:

- **Colorectal cancer**: 50–80%
- **Other cancers**:
  - Endometrial (very common)
  - Ovarian
  - Stomach
  - Small intestine
  - Pancreas
  - Brain
  - Renal pelvis and ureter

🧠 Key Features:

Feature	Lynch Syndrome (HNPCC)	FAP
Polyps	Few or none (nonpolyposis)	Hundreds to thousands
Cancer risk per polyp	High	Low
Typical mutation	DNA repair genes (MMR)	Tumor suppressor (APC)
Inheritance	Autosomal dominant	Autosomal dominant
CRC onset	~40s–50s	~30s–40s

Feature	Lynch Syndrome (HNPCC)	FAP
Other cancers?	Yes, many types	Less frequently

🔍 Sporadic vs. Inherited CRC (HNPCC)

- **HNPCC**: Germline mutations in MMR genes → inherited cancer predisposition.
- **Sporadic CRC with MSI**:
  - Often has **MLH1 hypermethylation** (not inherited)
  - MSI present, but not due to a germline mutation

🧠 Mnemonics to Help You Remember:

🧬 Genes & Functions:

"My Little Sister Helps Prevent Mistakes"

- **M**SH2
- **L**H1
- **S**H6
- **H**elps = PMS2
- **P**revent
- **M**istakes

⚖️ HNPCC vs. FAP:

"Few but Fatal" = HNPCC
"Many but Mild (initially)" = FAP

🧪 Clinical Relevance:

- **MSI Testing** and **Immunohistochemistry (IHC)** are used to detect Lynch syndrome in tumors.
- **Genetic testing** helps identify affected individuals and guide cancer surveillance for at-risk family members.
- **Surveillance and early screening** can greatly reduce cancer mortality in these families.

🧬 Inherited Breast Cancer Overview

✅ Family History and Risk

- Having a **first-degree relative** (like a mother or sister) with breast cancer **doubles your risk**.
- **1–3% of all breast cancer cases** are due to **inherited mutations**, mostly in **BRCA1 and BRCA2**.
- In families with multiple breast and ovarian cancer cases, these mutations account for **20–30%**, and even **60–80%** when both cancers are present.

🔬 BRCA1 and BRCA2 Genes – Normal Function

🧩 Role in DNA Repair

- BRCA1 and BRCA2 are **tumor suppressor genes**.
- Their proteins help repair **double-stranded DNA breaks** via a process called **homologous recombination** (HR).

🧬 How They Work:

1. DNA gets damaged (e.g., radiation).
2. Damage is detected by **ATM and CHEK2** kinases.
3. These kinases activate **BRCA1**.
4. **BRCA1** binds to **BRCA2**, which helps recruit **RAD51**.
5. **RAD51** repairs the DNA using the undamaged strand as a template.

💡 **Key partners**:

- **BRCA1** interacts with **p53**, **pRb**, and **Myc** to regulate the cell cycle, DNA repair, and apoptosis.

❌ What Happens When BRCA1/2 Are Mutated

🧬 Inheritance Pattern

- **Autosomal dominant**: You inherit **one mutated copy** from a parent.
- Cancer risk increases **when the second (normal) copy is lost** in some cells — the classic **"two-hit hypothesis."**

🔎 Mutation Characteristics

- Most BRCA mutations are:
  - **Nonsense**, **frameshift**, or **deletions**.
  - Result in **truncated**, nonfunctional proteins.

🔥 Consequence:

- Faulty DNA repair → **genomic instability** → **accumulation of mutations** → **cancer**.

📊 Cancer Risks Associated with BRCA Mutations

Mutation	Female Breast Cancer Risk	Ovarian Cancer Risk	Male Breast Cancer Risk
BRCA1	50–80%	40–50%	Modest increase
BRCA2	~50%	~20%	**70-fold** higher

🧠 **Note**: In **non-inherited (sporadic)** breast cancers, **BRCA mutations are rare**.

🧬 Genetic Testing Challenges

- **BRCA1 and BRCA2 are large genes** with **many possible mutations** (called **allelic heterogeneity**).
- DNA sequencing of **all coding and regulatory regions** is required, making testing complex.

🧠 Other Genes Linked to Inherited Breast Cancer

Besides BRCA1/2, mutations in the following genes also increase breast cancer risk:

Gene	Condition / Role
PTEN	Causes **Cowden syndrome**, increases breast cancer risk
ATM	Doubles breast cancer risk
PALB2	Works with BRCA1/2 to repair DNA
FGFR2	Increases breast cancer risk by ~25%

Even with BRCA1/2 and these other genes, they account for **less than 25% of inherited predisposition**. Many other genes contribute **small increases** in risk.

⚕️ Cancer Prevention in BRCA Mutation Carriers

Procedure	Purpose	Effect
Prophylactic oophorectomy (ovary removal)	After childbearing	↓ Ovarian cancer risk by **90%**, ↓ breast cancer risk by **50%**
Prophylactic mastectomy (breast removal)	Preemptive breast cancer prevention	↓ Breast cancer risk by **~90%**

These preventive surgeries are offered to **high-risk women** with BRCA mutations.

🧠 Summary Mnemonics:

🧬 BRCA Function:

"BRCA repairs Broken DNA with RAD51."

🧠 BRCA Mutation Cancer Risks:

- **B**reast, **R**epair gene
- **C**ancer in **A**ny gender: breast (♀ & ♂), ovarian, prostate, pancreas
- **1 = higher Ovarian**
- **2 = higher Male Breast**

🌞 Familial Melanoma – Overview

📈 Rising Incidence

- Melanoma (a dangerous skin cancer) rates have **increased dramatically** in the past 70 years, mainly due to **increased exposure to UV radiation** (e.g., sunlight, tanning beds).
- It's now **common**, with ~76,000 new cases each year in the U.S.

👨‍👩‍👧 Familial Risk

- **Family history** is a strong risk factor:
  - **1st-degree relative** with melanoma → **2x risk**
  - If they were diagnosed **before age 50** → **6x risk**
- Around **10% of all melanoma cases are inherited** (familial).

🧬 Key Gene in Familial Melanoma: CDKN2A

🔧 Normal Function of CDKN2A

- **CDKN2A** is a **tumor suppressor gene**.
- It produces two important proteins that **regulate the cell cycle**:
  1. **p16 (INK4A)**
     - Inhibits **CDK4/6** (cyclin-dependent kinases).
     - Prevents CDK4/6 from **phosphorylating and inactivating the pRb (retinoblastoma) protein**.
     - This keeps **pRb active**, which **blocks cell cycle progression** from G1 → S phase, stopping uncontrolled growth.
  2. **p14 (ARF)** (from an alternate reading frame of the same gene)
     - Stabilizes **p53** by **inhibiting MDM2**, a p53 suppressor.
     - Supports **DNA damage response** and **apoptosis**.

🧠 Think of CDKN2A as a **brake** for the cell cycle and a **guardian** of the genome.

❌ What Happens When CDKN2A is Mutated?

- In familial melanoma, **CDKN2A mutations** lead to **loss of p16 function**.
- Without p16:
  - CDK4 is **uninhibited** → it **inactivates pRb**.
  - pRb can't stop the cell cycle → **cells divide uncontrollably**, increasing cancer risk.

🧪 Mutation Stats:

- **20–40%** of familial melanoma cases have **CDKN2A mutations**.
- **~50%** of sporadic melanomas show **CDKN2A deletions**.
- **5–10%** have point mutations.
- **CDKN2A promoter hypermethylation** (epigenetic silencing) is also common in melanomas.

🧬 Another Familial Melanoma Gene: CDK4

- **CDK4** is a **proto-oncogene** (normal gene that can become cancerous if mutated).
- **Gain-of-function mutations** in **CDK4** → overactive CDK4.
- It **phosphorylates pRb too much**, inactivating it even if p16 is normal.
- This leads to **familial melanoma** via **cell cycle dysregulation**.

🔥 Key Somatic Mutations in Sporadic Melanomas

Gene	Mutation Type	Function	Effect
CDKN2A	Loss-of-function	Tumor suppressor	Cell cycle inhibition fails
BRAF	Gain-of-function	Kinase in **RAS/MAPK pathway**	Promotes **proliferation**
NRAS	Gain-of-function	GTPase in RAS pathway	Promotes **growth & survival**
TP53	Loss-of-function	Tumor suppressor	Disrupts DNA repair, apoptosis
RB1	Loss-of-function	Cell cycle checkpoint	Loss causes uncontrolled growth

🔬 About **50% of melanomas** have **BRAF mutations** → these tumors may respond to **BRAF inhibitors**.