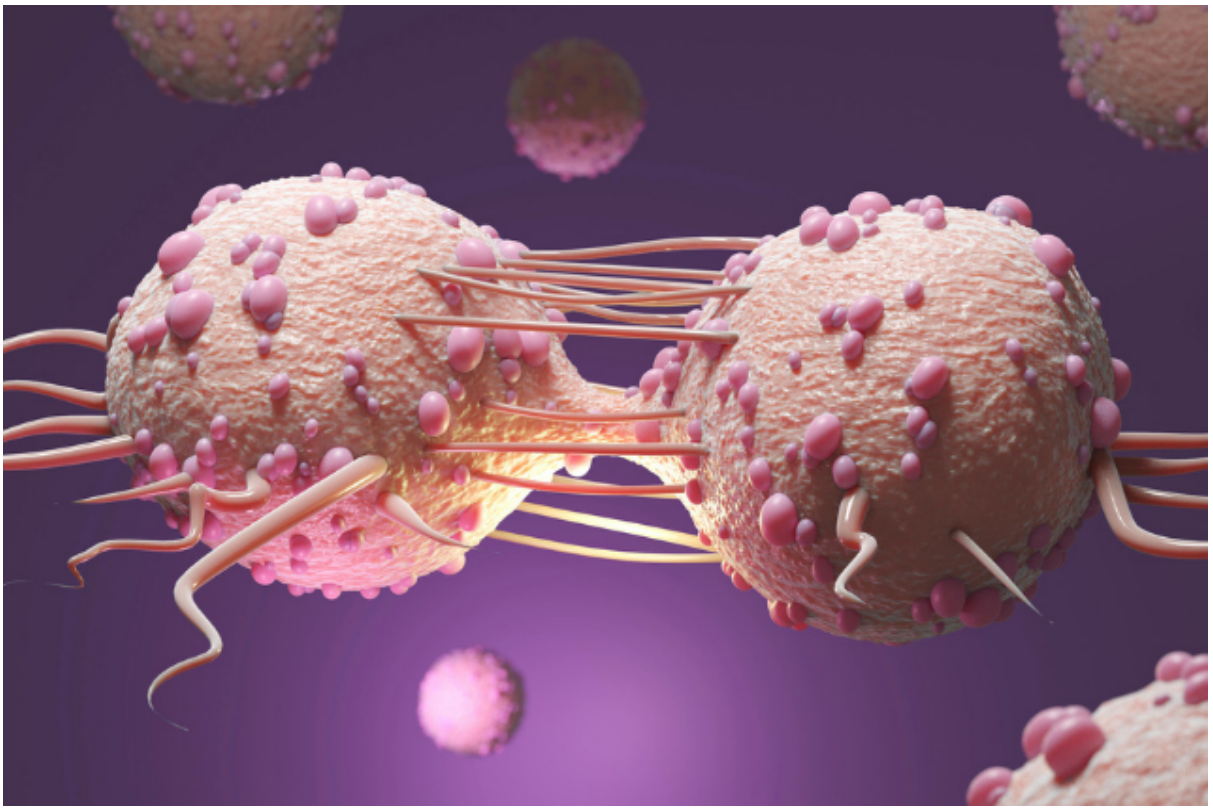
# Hereditary Cancer. How cancer is caused by inherited p53 gene mutations?



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# Hereditary Cancer - The Disease of Century: The inherited p53 structure, function, and predisposition


## Abstract

5% to 10% of all cancers are linked to gene mutations inherited from parents. The most common gene related to hereditary cancer is the p53 gene. It is a crucial tumor suppressor. However, the mutated gene is commonly inherited from one generation to another one. The functions of p53 resume to the activation when there are stress signals such as DNA damage, oncogene activation, etc. As a tumor suppressor, the p53 gene has 3 major functions: Cell cycle arrest, DNA damage repair, and Apoptosis. However, impairment or loss of p53 function can occur either by missense mutation, increased expression of negative regulators, or alterations in upstream/downstream pathways. A specific feature of mutant p53 is its gain-of-function (GOF) that promotes tumorigenesis. Hence, the inheritance of a TP53 mutation causes a predisposition to early-onset cancers. The most known inherited predisposition to a wide range of cancers due to the mutated p53 gene is Li-Fraumeni syndrome(LFS). In this review, it is discussed the role of inherited p53 gene mutations in the development of different cancers. However, research is still in progress on the inherited p53 predisposition and why some people with the inherited p53 gene have a higher risk to develop cancer. There is still no specific guideline for a variant of the germline TP53 gene.[5]



**Keywords:** Inherited cancer, p53 gene, Cell cycle arrest, DNA damage repair, Apoptosis, Gain-of-Function(GOF), Li-Fraumeni Syndrome


## Introduction

Cancer is the second pre-eminent cause of death globally (1 in 6 deaths). It can appear in each organ when abnormal cells grow uncontrollably and destructively; as a result, they can attack other body parts.[1] Occasionally, cancer is caused by mutations in certain genes passed from generation to generation.[2] Only about 5% to 10% of all cancers are known to be strongly linked to gene mutations inherited from parents. These cancers are often referred to as inherited cancers, what is actually inherited is the mutated gene that can lead to cancer.[3]

The p53 gene known as Tumor Protein 53 (TP53) is a crucial tumor suppressor and the most frequently altered gene which has a critical role in the development of cancer and cancer treatment with mutations being present in almost 50% of all invasive tumors. Moreover, in the most difficult-to-treat cancers (ovarian, breast, oesophageal,

cell lung cancers), p53 is mutated in at least 80% of the cases.[4] The goal of this review is to underline how inherited p53 mutations cause cancer.

## The structure of the p53 protein and gene description

The p53 gene is located on chromosome $17^{th}$(17p13.1). It is 20kb, consists of 11 exons, and encodes 393 amino acids. The p53 protein is a tetramer. The structure of each monomer includes "an N-terminal transactivation domain (TAD), a proline-rich domain (PRD), a core DNA-binding domain (DBD), a tetramerization domain (OD), and a C-terminal regulatory domain (RD)." (Figure 1) [5]

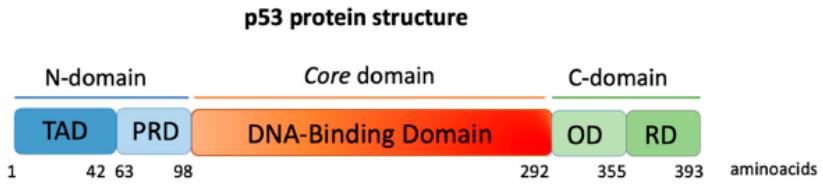


Figure 1. This figure is a representation of the domains which are included in the p53 protein structure. TAD - transactivation domain; PRD - proline-rich domain; DBD - DNA-Binding domain; OD - tetramerization domain; RD - regulatory domain. [5]

After more studies, it was demonstrated that p53 functions as a tumor suppressor. Stress signals such as DNA damage, oncogene activation, oxidative stress, and nutrient deprivation induce post-translational changes in p53 which result in its activation and accumulation in the cells. However, the Wild-Type and Mutant p53 proteins respond differently to stress signals which can be observed in Figure 2. [5]

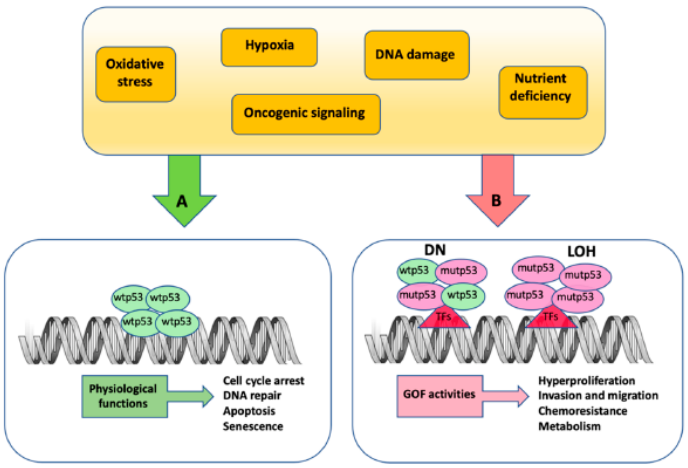


Figure 2. The response mechanisms of Wild-Type and Mutant p53 to stress signals. (A) - Scheme A shows the undertaken steps of Wild-Type p53. It activates specific pathways onto DNA sequences of target gene promoters. (B) - Scheme B shows the undertaken steps of Mutant p53. It forms oncogenic complexes with other transcription factors leading to activation of genes that have Gain of Function (GoF). Moreover, it also can be noticed that Mutant p53 can co-exist with Wild-Type p53 acting as a Dominant Negative(DN) factor, until the loss of the Wild-Type allele by Loss of Heterozygosity (LoH). [5]

In healthy cells, the p53 protein is in low amounts. However, stress signals may be responsible for the increasing level of p53 protein. When the amount is raised, the tumor suppressor function of the p53 protein often can respond in three ways: Cell-cycle Arrest, DNA damage repair, or Apoptosis (cell death). The initial TP53 -

mediated response to acute DNA damage is the induction of the G1 cell-cycle arrest which allows time for the detection and repair of DNA damage.[6] Firstly, during Cell-cycle arrest, the p21/WAF1 gene is induced, and p53 binds to two sites upstream of the p21 promoter. Then, the p21 mRNA is highly induced, and the first p53 target gene is isolated. Subsequently, p21 binds to **cyclin E/Cdk2 and cyclin D/Cdk4 complexes** – these **complexes** have the responsibility to bind to G1 and to help the cell cycle to move from G1 to S phase/DNA Duplication. – which cause G1 arrest in the cell cycle. The inhibition of Cdk4 and Cdk2 promotes transcription silencing of **E2F1** – a **gene** responsible for regulating the transcription of S phase cyclins and genes required for DNA replication.– which is critical for DNA replication and cell-cycle progression.[7] The cell-cycle arrest allows the DNA damage repair mechanisms such as nucleotide excision repair, base excision repair, and nonhomologous end-joining to occur. In certain cell types, activation of the TP53 protein can result in the induction of Apoptosis resulting in the elimination of irreversibly damaged cells.[6]

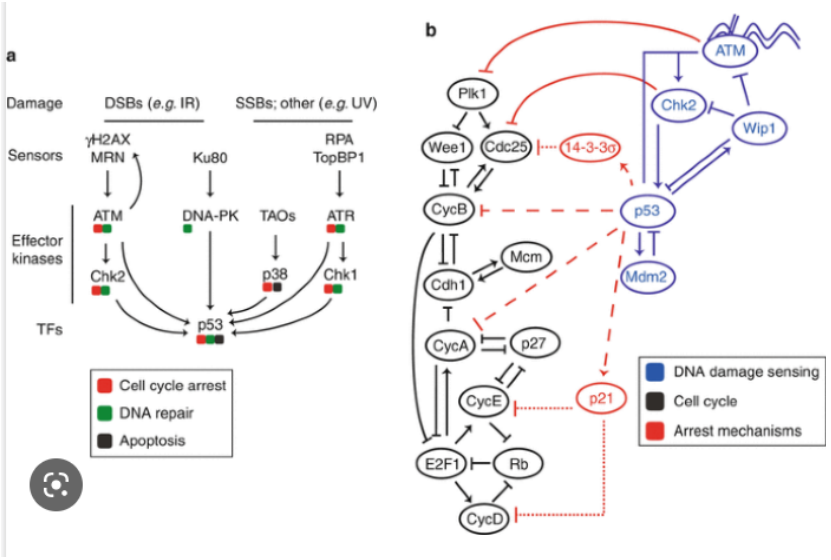


Figure 3. Schematical representation of Cell-cycle Arrest. p53 gene is induced when stress signals are detected, arrest mechanisms are induced. Then, the cyclin complexes are activated which causes G1 arrest in the cell cycle. The inhibition of cyclin complexes promotes transcription silencing of the E2F1 gene which is responsible for transcription regulation in S-phase cyclins and genes required for DNA replication. [8]

## Role of the p53 mutant

Impairment or loss of p53 function, however, is widespread in human malignancy. About 80% of the mutations are missense and full-length protein, which tends to accumulate to high levels in tumor cells.[5,9] A part of these mutations functions as a dominant negative (DN) or Wild-Type p53. This affects the tumor-suppressive pathways. Moreover, there can occur Loss of Heterozygosity of Wild-Type alleles. Most common mutations of p53 (R175, G245, R248, R273, and R282 (Table 1)) are located in the DNA-binding domain. (Figure 4) [5]

Table 1 | ***TP53* mutation frequency and most common mutations in different tumour types**

| Tumour type | *TP53* mutation frequency (%) | Most common *TP53* mutations* |
|---|---|---|
| Ovarian serous carcinoma | 94.6 | R273H=Y220C>R248Q>R175H |
| Lung squamous cell carcinoma | 79.3 | R158L>R175G>V157F=R213X=T125T |
| Head and neck squamous cell carcinoma | 69.8 | R175H=R273H=R213X=R282W>R248W |
| Glioblastoma | 28.3 | R248Q>R175H>R273H=R282W |
| Pan-cancer‡ | 42.0 | R175H>R273H>R248Q=R248W>R213X>Y220C |

**Table 1.** This table shows the most common mutations of p53 found in human malignancy. Mutations are ordered according to their frequency of occurrence. The '>' symbol is used to indicate that a mutation is more frequent than the following one, whereas '=' is used when two mutations occur at a similar frequency. With data from 10.000 tumors, the order of frequency of the TP53 mutations is: R273H>R248Q>R175H>R213X>G245S>R282W.[6]

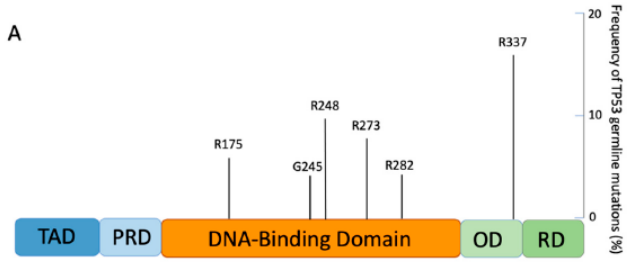


Figure 4. A representation of the 6 most common mutations that can be found in human malignancy of p53 in the DNA-binding domain.[5]

Generally, p53 mutations are classified as DNA contact mutations (R248Q, R273H) which affect the protein domains that are directly responsible for DNA binding, or as conformational mutations (R175H, H179R) which cause either a full or partial distortion of the correct folding of the DBD of the p53 protein.[5,9] A specific feature of missense mutations of p53 is its gain-of-function (GOF) that promotes tumorigenesis. GOF is remarked through various mechanisms such as increased proliferation, inhibition of apoptosis, resistance to chemotherapy, enhanced inflammation, drug resistance, angiogenesis, and invasiveness. All of them make a poor prognosis and a low rate of survival for patients.[5,9]

## Inheritance of mutated p53 gene and Predisposition

At present, there are investigated two main types of cancer. The first is Hereditary Cancer which develops due to a gene mutation that is present from birth. The second is Sporadic Cancer in which the gene mutations are acquired during the lifetime due to

lifestyle, environmental, and medical factors. Around 75-80% of cancer is sporadic. Moreover, the risk of getting sporadic cancer increases with age. (figure 4) [10]

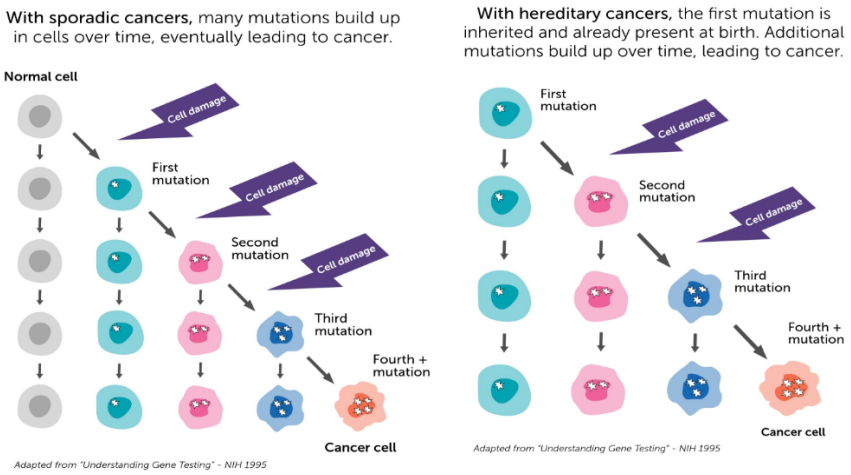


Figure 4. The difference between Sporadic Cancer (first/left illustration) and Hereditary Cancer (second/right illustration). [11]

Inheritance of a TP53 mutation causes predispositions to early-onset cancers including breast carcinomas, sarcomas, brain tumors, and adrenal cortical carcinomas, defining the Li-Fraumeni (LFS) and Li-Fraumeni-like (LFL) syndromes.[12] Additionally, there are some signs suggesting the possibility of the presence of hereditary cancer, for instance: early ages of cancer diagnosis, two or more relatives with the same type of cancer on the same family line, and, also, certain rare cancers are present.[13] The most known inherited predisposition to a wide range of cancers due to the mutated p53 gene is Li-Fraumeni syndrome(LFS). It has an autosomal dominant character, which results in a 50% possibility to inherit the mutated gene; therefore, there are substantially higher risks to develop cancer.[14] There have been reported commonly observed types of cancer observed in LFS such as premenopausal breast cancer, bone, and soft tissue sarcomas, adrenal cortical carcinoma, acute leukemia, brain tumor, and adrenal cortical tumors. Moreover, people with LFS typically develop cancer before 45 years old.[6,15] Therefore, the p53 gene is a cancer susceptibility gene because when it is inherited, it increases the risk of having cancer. A mutant copy of a cancer susceptibility gene can result in a lack of functional gene product which will lead to tumor formation. The p53 allele might be associated with high penetrance (the allele is highly expressed which means that the person will get a form of cancer) or reduced penetrance (the inherited mutated gene is not expressed in all organisms which results in a lower risk of getting a form of cancer).[16] Each mutation of p53 has its penetrance level. At this moment, the predisposition level depends on many causes: combined effects on multiple genes, lifestyle, and environmental factors,[17,18] that is why this domain is still being investigated. Nevertheless, cancer predisposition can be confirmed with molecular genetic testing. [16]

## Conclusion

In conclusion, the p53 gene is a crucial tumor suppressor in the development of cancer. It is highly present in difficult-to-cure cancers (ovarian, breast, cell lung). The precise molecular mechanism underlying TP53's tumor-suppressor function has not been defined yet and remains the focus of an active investigation. Getting more information on its functions will have a great impact on cancer biology understanding and on cancer therapy by knowing the specific vulnerabilities imposed on tumors by loss of TP53 function.[6] Therefore, the gene is still being researched. It is still unknown how the tumor-suppression part of the gene is involved in preventing the cancer cells to grow. However, research is still in progress on the inherited p53 predisposition and why some people with the inherited p53 gene have a higher risk to develop cancer. There is still no specific guideline for a variant of the germline TP53 gene.[5]

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