Nepal J Biotechnol. 2026 Jul; 14 (1): 72-79 Review Article DOI: https://doi.org/10.54796/njb.v14i1.466

Nepal Journal of Biotechnology
Publisher: Biotechnology Society of Nepal ISSN (Online): 2467-9313
Journal Homepage: https://nepjb.com/index.php/NJB ISSN (Print): 2091-1130

Genetic Determinants of Cancer development

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Received: 26 Nov 2025; Revised: 01 Jul 2026; Accepted: 07 Jul 2026; Published online: 31 Jul 2026

Abstract
The fundamental cause of cancer is an accumulation of genetic and genomic mutations that disrupt normal cellular homeostasis over time. Extensive research has established that mutations in oncogenes, tumor suppressor genes, and DNA repair genes, together with dysregulation of apoptotic pathways, play pivotal roles in tumor initiation, progression, and metastasis. These genetic abnormalities alter critical cellular processes, including cell proliferation, genomic stability, DNA damage response, and programmed cell death, thereby facilitating malignant transformation and disease progression. This review highlights the molecular mechanisms underlying the genetic determinants of cancer, emphasizing the contribution of inherited and acquired genetic alterations to carcinogenesis. It also discusses the interplay between diverse genetic factors and their impact on tumor heterogeneity. A comprehensive understanding of the genetic basis of cancer is essential for developing more effective therapeutic interventions and improving clinical outcomes in patients with diverse malignancies.

Keywords: Cancer, Genetics, Tumorigenesis, Apoptosis, Oncogenes, Mutations

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Introduction
Cancer is one of the most serious, fatal, and multifactorial diseases in the world. Over the past few years, cancer cases have been prevalent globally, causing the deaths of millions. While chemical carcinogens, radiation, and various environmental factors are often believed to be the main causes of cancer, these external agents actually act by triggering mutations in certain genes associated with cancer. These mutations, once present in the genes, drive the transformation of normal cells into cancerous ones. Alterations in the genes having the ability to develop into cancer cells when mutated and over expressed are acquired by organism in their lifetime because of environmental factors like phthalates, bisphenol A, etc., and in some cases, these genes get inherited from one generation to another, forming a chain of disease in every generation. In cancer, the somatic cells are mostly involved as compared to the germ cells. That's why they are also known as a somatic cell genetic disorder [1].

Broadly, there are two cancer-causing genes: the Oncogenes and the tumor suppressor genes. The cancer-forming genes, also known as Oncogenes, under circumstances like DNA methylation and genetic mutation, result in cancer development. These Oncogenes, upon getting triggered, are activated by environmental factors, leading to the conversion of normal cells into malignant ones. The tumor suppressor gene is a regulatory gene that regulates normal cell proliferation, apoptosis, etc., and does not lead to abnormal cells growing out in the body of an organism. Any kind of disruption in its regulation can lead to genetic diseases like cancer. The development of cancer involves a series of genetic changes within the somatic cells in the body of an organism, disrupting normal regulatory functions and mechanisms [2]. This review helps future researchers focus on the epigenetic and genetic mechanisms through which cancer evolves, emphasizing the role of oncogenes, tumor suppressor genes, and related factors. It also explains how mutations, methylation, and genetic alterations in somatic cells transform normal cells into malignant ones, developing more effective therapeutic interventions and improving clinical outcomes.

The Evolution of Tumor
Tumorigenesis is a very complex process. The generation of tumor involves three stages: Initiation, progression and metastasis. During initiation, normal cells often get induced by harmful carcinogen, radiations and mutations. This step initiates uncontrolled growth. The progression includes further mutation which helps in the proliferation and survival strategy of the tumor cells which helps them to escape from the security management of the tumor suppressor cell and programmed cell death. The ultimate step of tumorigenesis is the metastasis which means that these tumor cells will evade from one region to another through blood stream. **Figure 1** indicates the process through which cancer cells emerge out from normal proto oncogenic cells. The evidence suggests that every step of tumorigenesis is enclosed by the stromal cells,

extracellular matrix and tumor microenvironment [3]. These components form an interactive network around the tumor cells thus supporting them to grow, proliferate and to evade cells security system and become resistant to therapies. The Claudin protein family (CLDNs) consists of over 20 major proteins which are helpful in forming a barrier across cell making them aware about things passing in or out of them. Any kind of mutations in these barriers or junction can lead to the formation of tumor which eventually leads to cancer formation. For instance, Claudin like CLDN1 presence in brain supports the tumor suppressor process and any kind of mutation or deletion or changes in it can lead to brain cancer like glioblastoma. However, in case of both ovarian and pancreatic cancer the presence of the CLDN4 is seen and that too in excessive amount, suggests that it can be used as a new safe and nontoxic treatment of such cancers in the near future [4].

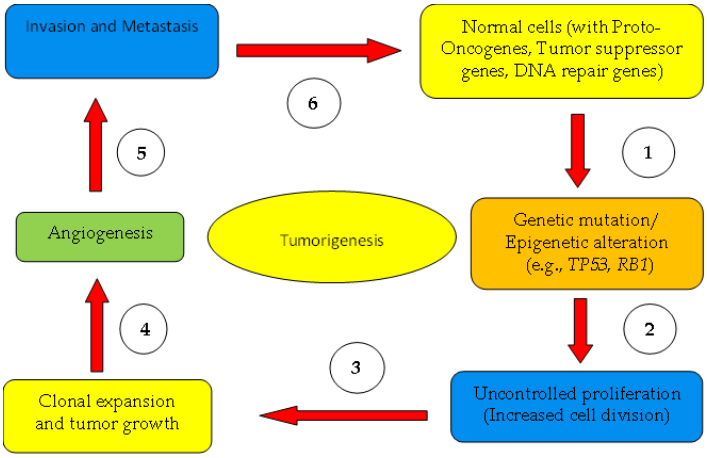

Figure 1: Involvement of tumorigenesis during cancer development

In research done by McFarland et al., it was found that cells that are not yet fully cancerous attain few mutations in them which drive them to survive the apoptosis, proliferate rapidly than normal cell thus forming a large population or colonies of them [5]. These uncontrolled behaviors of the precancerous cells push them toward the stage of becoming fully cancerous. Mitochondrial DNAs which are common in tumors play a noteworthy role in cancer initiation, progression and metastasis by disrupting the metabolic homeostasis [6]. Studies suggest that although there can be small genetic differences in the two cancerous cells but the mutation which cause cancer are usually same in all parts of the tumor and in its spread (metastasis) which makes the targeted treatment to work effectively [7]. There are eight hallmarks of cancer are there: Sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, including angiogenesis and activating invasion and metastasis, deregulating cellular energetic, avoiding immune destruction. Underneath all hallmarks two major factors, namely genetic instability and inflammation helps drive cancer proliferation [8].

Mutations: The Driving Force

Mutations are the main reason for cancer development. Be it somatic mutations or genetic mutations both lead to the fatal disease like cancer. There are many types of genetic mutation and they are point mutation, substitution, insertion, deletion, chromosomal aberration, copy number variation etc. From the cosmic database, it has been revealed that most common substitution occurs in the C-T, G-A and G-T nucleotide which results in the production of those type of codons which terminate the protein synthesis. Knowing this information would help to stop the formation of those types of stop codons. It has also been revealed that unlike insertion, deletions are more frequent in case of cancer with frameshift indels [9]. The inactivation or the mutation of tumor suppressor genes plays a key role in the process of tumorigenesis. There are many mechanisms through which it can be done including point mutations, insertion, deletion etc. Prior research revealed that tumor suppressor genes like *PTEN/MMAC1* (phosphatase and tensin homolog/Mutated in multiple advanced cancers 1) present in chromosome 10q23 remain inactivated during glioma, prostate and breast cancer due to point mutation and homozygous deletion [10]. Cheng et al. through copy number meta-analysis identifies 16 known tumor suppressor genes and proposed 27 new candidates, some of which such as *MGMT* (O^6-methylguanine - DNA methyltransferase), *RAD17* (RAD17 checkpoint clamp loader component) have previously established tumor the suppressive roles [11]. These emphasize how this mechanism can inactivate tumor suppressor genes and how the copy number Meta-analysis is essential in revealing new players in tumorigenesis. Usually, Somatic mutations are seen to be common in most cases of cancer as compared to the germ line mutation. These somatic mutations alteration occurs due to various environmental factors. Unlike genetic mutation the somatic mutation is not inherited but acquired by organism in their life time and it can be very dangerous. Somatic alteration impairs the crucial regulatory genes such as Oncogenes, DNA repair genes, tumor suppressor genes, etc., and then disrupts body's cellular homeostasis. When such important genes get impaired, they contribute to the disruption of normal cell cycle, DNA repair mechanism etc., and causing fatal diseases like cancer [12]. In comparison to somatic mutation, the

germ line mutation is inherited from parents to offspring and is present in every cell of the body as they are present in zygote, the very first cells of the body. Now these make such type of cancer very susceptible to familial cancer syndrome such as *BRCA1 and 2* (Breast Cancer gene 1 and 2) in case of breast and ovarian cancer which are two most common cancers in females [13]. Thus, it can be said that mutation of the driver key genes whether somatic or Germline, collectively contribute to various types of cancer as an outcome [14].

Somatic v/s Germline mutation

Genetic alterations associated with cancer are mainly classified as Somatic and Germline mutation. Somatic mutation occurs in non-reproductive parts of body during an individual's life time. While they remain confined to the affected cells, they are not inherited by offspring. They may contribute to sporadic cancers like lung cancer, oral cancers etc. In contrast to this Germline mutation occurs in germ cells and can be inherited by offspring. As a result, they are found to be present in all cells of organisms and increased the risk of hereditary cancers including those associated with *BRCA1* and *BRCA2* mutations. Therefore, while somatic mutations contribute to acquire cancers, the Germline mutations may underlie inherited cancer susceptibility.

The difference between somatic and Germline mutation is important from perspective of clinical intervention as it has its significant effects on the cancer diagnosis, risk assessment and treatment choices. The somatic mutation often act as the predictive bio marker for targeted therapies but Germline mutation can assess individual and families at higher risk for cancer. Improvements in next generation sequencing technologies have allowed for a detailed yet accurate analysis of both somatic and Germline changes, supporting precision oncology and enhancing patient's care [15]

Tumor Suppressor Gene: The Guardian of the Genome

The tumor suppressor genes are the crucial types of genes present in the body of an organism which regulate homeostatic balance between cancerous and non-cancerous cells. They encode some essential proteins which prevent uncontrolled cell division, and genomic instability. Like checkpoints, they maintain a regular checking on the tumor growth and ultimately suppress them. Any kind of mutation in them can cause the growth of tumors, uncontrolled cell division in the body which ultimately lead to cancer cells or the malignant cell's development. There are several types of tumor suppressor genes of which *Tp53* and *RB1* are the main one [16]. The *Tp53* is actually a tumor suppression factor which suppresses those transcripts which have the ability to form cancerous proteins later on. The *Tp53* gene encodes p53 protein, a transcription factor which takes part in DNA repair, cell cycle arrest and in apoptosis also. Mutation in it is commonly found in case of 50% cancers. The Germline mutation in *TP53* can lead to the disease called Li-Fraumeni syndrome [17], [18]. The transition between the G1 and S phase of the cell cycle is controlled by *RB1* gene. The *RB1* is identified as the first tumor suppressor gene whose mutation can cause pediatric retinoblastoma cancer in children. Very small mutations dominate somatic and germ line mutations in *RB1* gene [19]. According to Knudson's two hit hypothesis, tumor suppressor gene like *RB1* need inactivation of both alleles for the advancement of tumor growth to malignant one. In case of hereditary retinoblastoma, one defective *RB1* allele is inherited from the germ line mutation whereas other one from the somatic mutation. In contrast, sporadic retinoblastoma arises when both mutational events occur somatically within the same cell. The *RB1* has therapeutic significance, as tumors having functional *RB1* shows quick respond to CDK4/6 inhibitors as compared to those tumors that lacks RB1 and becomes resistance to these targeted therapies [20].

Defects in DNA repair Genes

The DNA repair genes help in repairing of the DNA. All total 130 DNA repair genes are known to be described till now [21]. These DNA repair genes are vital for the protection of genome stability [22]. The DNA repair genes protect the cellular DNA from the continuous attack of the reactive species and environmental agents inside the cell. Therefore, any kind of defects in them can lead to the defects in the DNA. Unsuccessful protection from this damage can lead to the various types of diseases like cancer. When the DNA repair gene gets defected, cancer cell starts to build up the genetic instability, which contributes to the aggressive phenotype of the cancer [23]. In advanced cells like eukaryotic cells, there are many mechanisms through which the DNA repair genes repair or correct the DNA sequences. In humans, such mechanisms include modification of bases, breaking of double stranded breaks, DNA crosslinks, etc. Apart from this there are other mechanisms like direct reversal, base excision repair, nucleotide excision repair etc. In base excision repair mechanism, single damaged bases are removed using the DNA glycosylases and AP endonucleases whereas in case of nucleotide excision repair process, massive lesions like UV induced photoproducts are removed by excising 25-32 long

Table 1: Major DNA Repair pathways, key genes, and their clinical Implications

DNA repair pathway	Type of DNA damage repaired	Key Genes/Proteins involved	Function	Associated Disorders/Cancers
Direct repair	Base modifications	*MGMT*	Removes alkyl groups from damaged DNA bases	Glioblastoma, colorectal cancer; MGMT promoter methylation predicts response to temozolomide
Base excision repair (BER)	Single damaged bases	*MUTYH, OGG1, APE1, PARP1*	Repairs small base lesions caused by oxidation, alkylation, or deamination	Mutation accumulation, cancer predisposition
Nucleotide Excision Repair (NER)	Bulky DNA lesions, UV-induced photoproducts	*XPA-XPG* (Xeroderma pigmentosum complementation group A-G)	Repairs bulky DNA adducts and UV-induced DNA damage	Xeroderma pigmentosum, trichothiodystrophy, skin cancer
Double strand break repair	DNA double strand breaks	*BRCA1, BRCA2*	Repairs breaks in both DNA strands to maintain genomic stability and prevent chromosomal abnormalities	Breast and ovarian cancer
Mismatch Repair (MMR)	Replication errors	*MLH1, MSH2, MSH6, PMS2*	Corrects replication errors such as base mismatches and insertion/deletion loops	Lynch syndrome, colorectal, endometrial, and gastric cancers
DNA crosslink repair	DNA crosslinks	DNA repair complexes	Coordinates the recognition and removal of DNA crosslinks and collaborates with NER and HRR pathways to restore DNA integrity.	Genomic instability
Chromatin associated repair	Complex DNA lesions	Multiple repair proteins	Remodels chromatin structure to provide repair proteins access to damaged DNA and facilitates efficient DNA repair.	Aggressive tumor phenotypes
Homologous Recombination Repair (HRR)	DNA double strand breaks (DSBs), collapsed replication forks	*BRCA1, BRCA2, RAD51, PALB2*	Repairs DNA double stand breaks using a homologous template	Breast, ovarian, pancreatic, and prostate cancers
Non-Homologous End Joining (NHEJ)	DNA double strand (DSBs)	*KU70, KU80,* DNA-PKcs, *XRCC4, LIG4*	Repairs DNA double strand breaks without a template	Genomic instability; hematological malignancies
Fanconi Anemia Pathway	DNA interstrand crosslinks (ICLs) that block replication and transcription	*FANCA, FANCB, FANCC, FANCD2, FANCI*	Repairs DNA interstrand crosslinks	Fanconi anemia; leukemia and solid tumors
Translesion synthesis (TLS)	DNA lesions that stall replication forks(e.g., UV-induced lesions bulky adducts)	*POLH, POLK, REV1, REV3L*	Allows replication across damaged DNA templates	Increased mutagenesis and cancer susceptibility

nucleotide segments with the help of many proteins. Any kind of defects in these mechanisms can lead to genetic disorders like Xeroderma pigmentosum (XP), Trichothiodystrophy, etc. [24]. In **table 1**, all the DNA repair pathways, different types of damaged repair and the diseases associated with it are discussed. This table shows how defects or mutation in the DNA repair pathway can lead to the different types of diseases and cancers. People having XP are very vulnerable of developing skin cancer because their skin cannot repair the damaged DNA caused by UV rays. In the same way *BRCA1/2* are also the two DNA repair genes and any kind of mutation, alteration or defects in them can lead to the development of breast cancer and ovarian cancer. On the other hand, there are some genes called mismatch repair genes (MMR) like *MLH1* (MutL homolog 1), *MSH2* (MutS

homolog 2), etc. The mutations in any of these genes can result in the development of lynch syndrome, which is said to be responsible for the approx. 3% colorectal cancer cases. Therefore, DNA repair genes are said to be the crucial genes present in the body of an organism, which protects and guards normal cells from developing into the cancerous cells.

Epigenetic regulation

Till now it has been discussed how various ways through which genetic alteration occurs and how they ultimately contribute to the development of cancer. However, it is not known that there are some pathways which can cause the risk of cancer and that too without DNA mutation. These pathways or process can be summarized as epigenetic regulation or epigenetic pathways which altered gene expression without mutating the DNA sequences. When there is an inheritable change in gene expression without any mutation in the DNA sequences then that condition is defined as the epigenetics [25]. Importantly, genetic and epigenetic deregulations are not the independent events but are closely interconnected. Genetic alteration in key regulatory genes can disrupt epigenetic machinery, while epigenetic changes can silence tumor suppressor genes, impair DNA repair mechanisms, and promote genetic instability, thereby increasing the accumulation of further genetic mutations. This bidirectional interaction creates a self -reinforcing loop that drives oncogenic transformation and tumor progression. The accumulation of genetic alteration, which impacts the genomic structure and function, also caused oncogenic processes. The epigenetic modification includes the DNA methylation, histone modification, chromatin remodeling, etc., which work along with genetic mutation and influence gene expression, promoting tumor growth and spreads which ultimately lead to cancer [26]. They do so by silencing the tumor suppressor gene and at the same time by activating the oncogenic genes. In case of DNA methylation, methylation of CpG dinucleotide leads to gene silencing. Hypermethylation of tumor suppressor genes such as *BRCA1* lead to various types of cancer especially the breast and ovarian cancer. This epigenetic silencing results in impaired DNA repair functions, contributing to genomic instability and tumor development. Mutation in the chromatin remodeling genes such as *SMARCB1, PBRM1* etc., frequently lead to various types of cancer such as rhabdoid tumors, ovarian clear cell carcinoma, renal cell carcinoma etc. The inappropriate expression or repression of some genes which results from epigenetic modification can disrupt normal function of cell and lead to the formation of tumors. High levels of enzymes which act as epigenetic modifiers are found to be associated with the aggressive as well as metastatic breast cancers, thus contributing to recurrence and poor diagnosis. Earlier only the genetic changes were considered for cause of cancer but now the epigenetic causes are also being considered because they also play an important role in tumorigenesis. In recent studies, it has been found that behind the development of many types of tumors there is a role of the epigenetic modification and not genetic changes only. The particular DNA methylation can result in Beckwith-Wiedemann syndrome which is branded by congenital anatomic malformations accompanied by a strong predisposition to cancer [27].

Apoptosis

Apoptosis can be defined as the regulated destruction of a cell or vital physiological process of cell death. It is essential for the elimination of damaged and abnormal cells from body of an organism thus maintaining cellular homeostasis. This regulated self-destruction is essential for development, immune function and tissue remodeling. After doing research, many scientists found that the process of apoptosis has to occur in very accurate rate in body. Too much or too little of this process can cause serious consequences, of which too little can lead to cancer formation also where abnormal cells do not die. The apoptosis is tightly regulated by pro-apoptotic (e.g., *BAX, BAK*) and anti-apoptotic genes (e.g., *BCL-2, BCL-XL*). There are two major pathways through which apoptosis occur viz are Intrinsic (Mitochondrial) and Extrinsic (Death receptor) pathways. The intrinsic pathway which is controlled by the B-cell lymphoma 2 (BCL-2) families of proteins is conserved from worms to humans and is important for normal development of cells [28]. The intrinsic pathway occurs in the mitochondria. In case of stressed cells, the proapoptotic BCL-2 proteins caused the permeabilization of the mitochondrial outer membrane (MOMP) which results in release of Cytochrome c (Cyt c) into cytoplasm. This led to the formation of apoptosome, a protein complex which activates caspase-9, triggering cell death. On the other hand, in extrinsic pathway the death receptor such as CD95, TRAIL-R1/2, upon binding to their ligands form the death-inducing signaling complex (DISC), leading to activation of initiator caspases like caspases-8 and, subsequently, executioner caspases. Any kind of mutation or down regulation in the DISC can result in tumor formation and cancer like diseases [29]. Therefore, current therapeutic strategies aim to restore apoptosis, including BH3 mimetic like venetoclax that inhibit BCL2

and reactivate the intrinsic pathway, p53 reactivation therapies, death- receptor targeting drugs, and conventional chemotherapy and radiotherapy that induce DNA damage and trigger apoptosis, making enhancement of apoptotic pathways a key approach in modern cancer treatment. Apoptosis is closely linked to tumor suppressor genes, particularly p53, which induces apoptosis in response to DNA damage. Mutation or loss of p53, a frequent event in many cancers, impairs this apoptotic response and promotes accumulation of oncogenic mutations. Additionally, defects in death receptor signaling and caspases activation further contribute to resistance to apoptosis in cancer cells. Thus, failure of apoptotic mechanisms due to genetic alterations is a key factor in tumor initiation, progression, and resistance to cancer therapy [30].

Genetic Alterations in Different types of Cancers

There are various types of genes which are responsible or behind the development of different types of cancer. Mutations in different genes lead to formation and progression of different cancers. Like in case of breast cancer not only the *BRCA1* or 2 gene but also the genes like *TP53, PALB2* (Partner and Localizer of BRCA 2), *CDH1* (Cadherin 1), *STK11* (Serine/Threonine Kinase 11), etc., are responsible for its development. Mutations in *BRCA1, BRCA2, PALB2, CDH1*, and *STK11* are typically Germline mutations, predisposing individuals to heredity breast cancer, whereas *TP53* mutations are mostly somatic, although Germline *TP53* mutations are observed in rare hereditary cancer syndromes such as Li-Fraumeni syndrome [31].

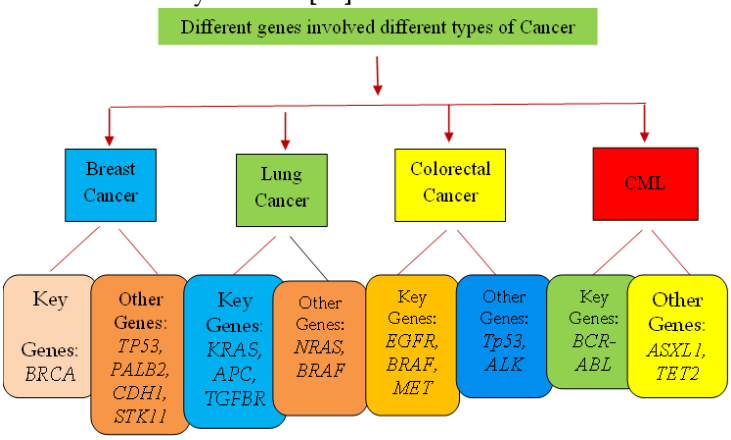

Figure 2. Possible involvement of different types of genes in Cancer Biology.

In case of colorectal cancer which is the third most worldwide cancer in men as well as second most common in women, genetic alteration includes activation of proto-oncogenes such as *KRAS* (Kirsten rat sarcoma viral oncogene homolog), loss of *APC* (Adenomatous polyposis coli), mutations in *TP53* and loss of heterozygosity (LOH) of long arm of chromosome 18, mutations of *TGFBR* (Transforming Growth Factor Beta Receptor) and *PIK3CA* gene. These genetic alterations are predominantly somatic mutations acquired during Tumor progression. Additionally, genes such as *NRAS* (Neuroblastoma RAS Viral (v ras) oncogene homolog), *BRAF* (B-Raf proto-oncogene, serine/threonine kinase) genes are also involved in colorectal cancer. Lung cancer, which is often thought to be caused by the tobacco smoking, is much more than that. Lots of genes play a role in its development. There are many genes which protect the proto-Oncogenes from their development into the Oncogenes and mutations in those genes cause lung cancer. Specifically in non-small cell lung carcinoma (NSCLC), somatic mutations in *EGFR* (Epidermal Growth Factor Receptor), *BRAF, MET* (MNNG HOS transforming gene), alterations and gene rearrangements, and *KRAS* point mutations are common along with the *Tp53*, *ALK* (Anaplastic Lymphoma Kinase). Studies analyzing lung cancer cell lines have further shown that *TP53* and either CDKN2A or *RB1* are inactivated in majority of cases, while alterations in *BRAF, MET, ERBB2,* and *NRAS* occur less frequently. Multiple signaling pathways often converge on the mTOR pathway, and tumors harboring simultaneous pathway activations tend to be less responsive to single-agent targeted therapies, highlighting the need for combination therapeutic approaches [32]. Chromosomal translocation which is the most common feature of genetic alteration can be seen in hematological malignancies, such as *BCR-ABL* (Break point Cluster Region – Abelson Murine Leukemia Viral Oncogene Homolog 1) fusion in chronic myeloid leukemia (CML). In case of CML, cancer is driven through constant tyrosine kinase activity. This fusion is a somatic mutation arising in hematopoietic cells. Other than those genes like *ASXL1* (Additional Sex Combs Like1), *TET2* (Ten Eleven Translocation 2), etc., are also involved. **Figure 2** indicates how different types of genes present in our body are responsible for different types of cancer. Usually these many genes are responsible for control and prevention of various cancers but mutation in them can lead to the outbreak of different types of cancer as shown below in CML and are somatic in nature. Thus, it can be said that not only one but many types of genes are correlated with the formation and development of one type of cancer. In other words, it can be said that different cancer harbors different genetic mutations, which reflect the genetic heterogeneity among them. This mutation in the genes

displays not only the genetic heterogeneity but also guides us about the way they work in the body of an organism and help us in tailoring personalized medicines and targeted therapy.

Conclusion

Cancer is a multifactorial disease and often includes genetic mutations for its development. Genetic research and the study of genetics role in cancer have reshaped and widen our knowledge about cancer. It is not seen as a disease arising from a single cause but with lots of genetic as well as epigenetic alteration. It has been studied how mutation, defects in DNA repair genes, dysregulation of apoptosis lead to the formation of tumorigenesis. Studies suggest that mutations in different genes in case of various cancers have shifted cancer research from generalized model to the targeted therapy. In the near future despite every challenge future investigation could address tumor heterogeneity, resistance mechanism of cancer in order to gain early and equitable access to precision oncology. Despite many progressions in cancer biology there are still some genes left whose mutation can result in cancer progression. As a result, this kind of research on their genes may contribute to the development of more effective personalized treatment plans and ensure that everyone has equal access to precise cancer care. It may also help to better understand tumor differences and how they resist treatment.

Authors' Contributions

Conceptualization, PU and RKU; writing – original draft preparation, PU; writing – review and editing, RKU and PU; supervision, RKU. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest:

The authors declare no conflict of interest.

Funding:

The author received no financial support for the research, authorship, and/or publication of this article. This work was done without any commercial or financial interests. It is purely intended to support education.

References

[1] Stoler, AB., Genes and Cancer. British Medical Bulletin; 1991, 47(1), 64-75. doi: 10.1093/oxfordjournals.bmb.a072462

[2] Balmain, A. The critical roles of somatic mutations and environmental tumor-promoting agents in cancer risk. Nat Genet 2020, 52, 1139-1143. doi: 10.1038/s41588-020-00727-5

[3] Wang, M., Zhao, J., Zhang, L., Wei, F., Lian, Y., Wu, Y., et al., Role of tumor microenvironment in tumorigenesis. Journal of Cancer. 2017, 8(5), 761. doi: 10.7150/jca.17648.

[4] Swisshelm, K., Macek, R., Kubbies, M., Role of claudins in tumorigenesis, Advanced drug delivery reviews 2005, 57(60), 919-928. doi: 10.1016/j.addr.2005.01.006

[5] McFarland, CD., Mirny, LA., Korolev, KS., Tug-of-war between driver and passenger mutations in cancer and other adaptive processes. Proceedings of the National Academy of sciences 2014, 111(42), 15138-15143. doi: 10.1073/pnas.1404341111.

[6] Kim, M., Mahmoud, M., Reznik, Ed., Gammage, PA., Mitochondrial DNA is a major source of driver mutations in cancer. Trends in Cancer 2022, 8(12), 1046-1059. doi: 10.1016/j.trecan.2022.08.001.

[7] Reiter, JG., Baretti, M., Gerold, JM., et al., An analysis of genetic heterogeneity in untreated cancers. Nature Reviews Cancer 2019, 19(11), 639-650. doi: 10.1038/s41568-019-0185-x

[8] Hanahan, D., Weinberg, RA., Hallmarks of Cancer: the next generation. Cell 2011, 144(5), 646-674. doi: 10.1016/j.cell.2011.02.013.

[9] Lengar, P., An analysis of substitution, deletion and insertion mutations in cancer genes. Nucleic Acids Research 2012, 40(14), 6401-6413. doi: 10.1093/nar/gks290.

[10] Cairns, P., Evron, E., Okami, K., et al., Point mutation and homozygous deletion of PTEN/MMAC1 in primary bladder cancers. Oncogene, 1998. 18; 16 (24), 3215-3218. doi: 10.1038/sj.onc. 1201855.

[11] Cheng, J., Demeulemeester, J., Wedge, DC., et al., Pan-cancer analysis of homozygous deletions in primary tumours uncovers rare tumour suppressors. Nature Communications, 2017, 8(1), 1221. doi: 10.1038/s41467-017-01355-0

[12] Stratton, MR., Campbell, PJ., Futreal, PA., The cancer genome. Nature 2009, 458 (7239), 719-724. doi: 10.1038/nature07943

[13] Miki, Y., Swensen, J., et al., A strong candidate for the Breast and Ovarian Cancer Susceptibility Gene *BRCA1*. Science 1994, 266 (5182), 66-71. doi: 10.1126/science.7545954.

[14] Beichman, CA., Zhu, L., Harris, K., The evolutionary interplay of somatic and Germline mutation rates. Annual Review Biomedical Data Science 2024, 7:83-105. doi: 10.1146/annurevbiodatasci-102523-104225.

[15] Ramroop, JR., Gerber, MM., Toland, AE., Germline variants impact somatic events during tumorigenesis. Trends in Genetics 2019, 35: 515-526. doi: https://doi.org/10.1016/j.tig.2019.04.005

[16] Donehower, L., Soussi, T., Integrated analysis of *TP53* gene and pathway alterations in the cancer genome atlas. Cell Reports 2019, 28(5), 1370-1384. doi: 10.1016/j.celrep.2019.07.001.

[17] Foo, T K., Tischkowitz, M., et al., Compromised *BRCA1-PALB2* interaction is associated with breast cancer risk. Oncogene, 2017, 36 (29), 4161-4170. doi: 10.1038/onc. 2017.46

[18] Frebourg, T., Bajalica, S., et al., Guidelines for the li-Fraumeni and heritable *TP53*-related cancer syndromes. European Journal of Human Genetics 2020 28(10), 1379-1386. doi: 10.1038/s41431-020-0638-4

[19] Lohmann, DR., *RB1* gene mutations in retinoblastoma. Human Mutation 1999, 14(4), 283-288. doi: 10.1002/(SICI)1098-1004(199910) 1

[20] Knudson, A.G., Hereditary cancer: Two hits revisited. Journal of Cancer Research and Clinical Oncology 1996, 122, 135-140. doi: 10.1007/BF01366952

[21] Wood, RD., Mitchell, M., Sgouros, J., Lindahl, T., Human DNA repair genes. Science 2001, 291:1284-1289. doi: 10.1002/em.1033

[22] Ronen, A., Glickman, BW, Human DNA repair genes. Environmental and Molecular Mutagenesis 2001, 37(3), 241-283. doi: 10.1002/em.1033.

[23] Dietlein, F., Thelen, L., Reinhardt, HC, Cancer- specific defects in DNA repair pathways as targets for personalized therapeutic approaches. Trends in Genetics 2014, 30(8), 326-339. doi: 10.1016/j.tig.2014.06.003.

[24] Tuteja, N., Tuteja, R, Unraveling DNA repair in human: molecular mechanisms and consequences of repair defect. Critical Reviews in Biochemistry and Molecular Biology 2001, 36(3), 261-290. doi: 10.1080/20014091074192.

[25] Chen, QW., Zhu, XY., Li, YY., Meng, ZQ., Epigenetic regulation and cancer. Oncology Reports 2014, 31 (2), 523-532. doi: 10.3892/or.2013.2913.

[26] Baxter, E., Windloch, K., Gannon, F., Lee, LS. Epigenetic regulation in cancer progression. Cell and Bioscience, 2014, 4(1), 45. doi: 10.1186/2045-3701-4-45

[27] Kelly, D A., Issa J., The promise of epigenetic therapy: reprogramming the cancer epigenome. Current Opinion in Genetics and Development 2017, 42, 68-77. doi: 10.1016/j.gde.2017.03.015.
[28] Wu, CC., Bratton, SB., Regulation of the intrinsic apoptosis pathway by reactive oxygen species. Antioxidants and Redox Signaling 2013, 19(6), 546-558 doi: 10.1089/ars.2012.4905.
[29] Verbrugge, I., Johnstone, RW, Smyth MJ., Snapshot: extrinsic apoptosis pathways. Cell 2010, 143 (7), 1192-1192. doi: 10.1016/j.cell.2010.12.004
[30] Kale, J., Osterlund, E. & Andrews, D. BCL-2 family proteins: changing partners in the dance towards death. Cell Death Differ 2018, 25, 65–80. doi:10.1038/cdd.2017.186
[31] Guha, T., Malkin D., Inherited *TP53* mutations and the Li-Fraumeni syndrome. Cold Spring Harbor Perspectives in Medicine 2017, 7(4), a026187. doi: 10.1101/cshperspect.a026187.
[32] Blanco, R., Iwakawa, R., Tang, M., et al., A gene-alteration profile of human lung cancer cell lines. Human Mutation 2009, 30(8), 1199-1206. doi: 10.1002/humu.21028.