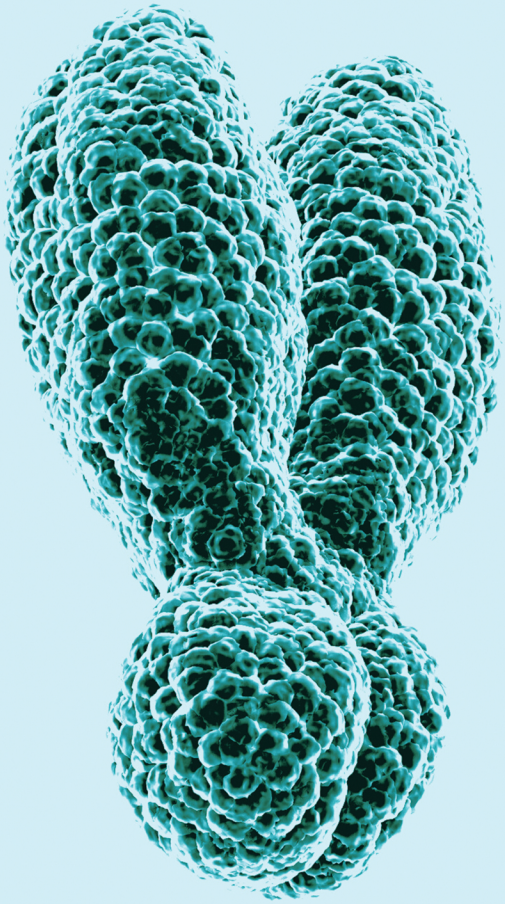
A COMPILATION OF GENES IN EACH CHROMOSOME

CANCER GENES



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FOREWORD

The collection of diseases known as cancer has been recognized as a deadly disease for more than 4000 years. Amazing improvements in the treatment of cancer have occurred in the past century. Still, however, understanding the molecular basis of cancers' origins remains incomplete. Neoplasms are complex diseases that involve mutations or aberrant expression of dozens of genes. The pace of cancer genetics research has expanded exponentially following the sequencing of the human genome. While a tremendous boon for cancer researchers, there have been numerous missed opportunities because the overwhelming numbers of papers published make it nearly impossible for any cancer researcher to keep up.

Dr. Satish Ramalingam and colleagues provide this extensive compendium of cancer genes. The catalog summarizes key data which implicates each gene in one or more cancers and summarizes key studies that explore each mechanism of action. The organization, by the chromosomes on which the genes are encoded, allows both experts and neophytes to cross-reference and facilitate their research objective(s).

The monograph is a compendious primer that will be a valuable resource for cancer biologists, clinical oncologists and students engaging in basic discovery, translational research, or clinical treatment of cancer.

Danny R. Welch, PhD
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PREFACE

Cancer incidence is rising and has become a leading cause of death in many cities worldwide. It is well documented that cancer initiation and progression depend on the genes expressed in the cell's genome. It is imperative to understand the genetics of this dreaded disease to win the war against it. As we attempted to understand the latest update about all cancer-related genes in all the chromosomes, we noticed a clear lacuna because no books cover all the important genes that play a role in cancer presented chromosome-wise for easy understanding. We have decided to fill the gap and compiled most of the genes that are identified to play an important role in cancer. We delve into the world of cancer-causing genes and their location on each chromosome. This book will provide valuable mechanistic insights about the mutations and dysregulation of cancer genes that provide an advantage for cancer cell survival during each stage of tumorigenesis. This volume provides a comprehensive overview of the cancer-causing genes located on chromosomes 1-12 and serves as an invaluable resource for researchers, medical professionals, and anyone interested in the genetic basis of cancer.

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CHAPTER 1

Chromosome 1

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Abstract: Chromosome 1 is the largest human chromosome, constituting approximately 249 million base pairs. Chromosome 1 is the largest metacentric chromosome, with "p" and "q" arms of the chromosome almost similar in length. Chromosome 1 abnormalities or inclusion of any mutations leads to developmental defects, mental, psychological, cancer, *etc*., among the most common diseases. $1/10^{th}$ of the genes in chromosome 1 have been reported its involvement in cancer growth and development. These cancer genes result from chromosomal rearrangement, fusion genes, somatic mutations, point mutation, gene insertion, gene deletion, and many more. Some of these cancer-causing genes appear to be involved in cancer more often, and other novel genes are also enlisted in this chapter.

Keywords: Cancer, Developmental defects, Fusion gene, Gene, Gene insertion, Gene deletion, Metacentric, Mutation, p-arm, Point mutation, Psychological, q-arm, Somatic mutation.

1. INTRODUCTION

Chromosomes are the large chunk of hereditary material that carries information from four nucleotides. This together makes a list of instructions for making proteins, regulatory elements, and other nucleotides required to maintain the growth and normal development of the cells. A human cell constitutes 22 pairs of autosomes and two sex chromosomes, one from each parent. Chromosome 1 is the largest human chromosome, with about 249 million long DNA base pairs, representing about 8% of the total DNA in cells. Chromosome 1 likely contains 2000 to 2100 genes that function cooperatively to achieve the existence of a well-functioning cell. Since we know there are approximately more than 2000 genes coded in chromosome 1 alone, we take a deep look into how many are reported to be involved in cancer disease. The Atlas of Cancer Genetics and Cytogenetics in Oncology and Haematology is a freely available database where all the inform-

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ation about the genes involved or has been reported for the cancer disease is updated regularly.

The list involves the proteins, microRNA, long non-coding RNA, *etc*., which are now included in the list. Among the 2000 genes on chromosome 1, 1/10th of its dynamic cancer growth and development have been reported. Out of these many genes, we have listed here some t, some top-notch genes that are repeatedly coming into the limelight and showing involvement in cancer.

1.1. MUC1: Mucin-1 Chromosome 1; 1q22

MUC1 protein is widely studied, and its expression is increased in various cancer types like breast, pancreatic, colon, *etc*. Human MUC1 protein is translated as a long single polypeptide, which auto cleaves into two subunits resulting in the formation of a non-covalent heterodimer. The MUC1-N subunit is expressed at the cell surface by forming a complex with the MUC1-C cytoplasmic subunit located in the cytoplasm [1]. Under typical situations, this assembly helps define polarity and create a protective mucous barrier in specialized organs, gastrointestinal and respiratory tracts, or lumen lining ducts. In a different scenario of stress conditions, the cell's polarity is lost, and the MUC1 protein is now positioned everywhere. MUC1-C cytoplasm domain is a 72 amino acid-long polypeptide and consists of various motifs which play an essential role in signaling. One of the binding motifs is CQC which is necessary to form a MUC1-C oligomer. The oligomerization process is critical for transporting MUC1-C to the nucleus and further its interaction with importin β, which helps transport MUC1-C to the nucleus. Inside the nucleus, MUC1-C associates with p53, β-catenin/TCF4, estrogen receptor α [ERα], NF-κB p65, and STATs. In MUC1-C, phosphorylation of the YEKV site induces the binding of β-catenin to the SAGNGGSSLS sequence. This stabilizes the β- catenin and activates Wnt target genes, such as *cyclin D1* and CTFG. The cytoplasm subunit MUC1-C interacts with receptor tyrosine kinases [*e.g*., ErbB1- 4] and participates in downstream signaling pathways activating EGFR, FGFR3, PDGFRβ, and Met [2, 3]. MUC1-C tail domain also starts EZH2 and BMI1 in triple-negative breast cancer epigenetic reprogramming. MUC1-C interacts with MYC and selectively activates the MTA1 and MBD3 genes. These are components of NuRD signaling. This results in the activation of the NuRD complex and drives dedifferentiation and reprogramming of triple Negative Breast Cancer Cells [4].

1.2. NTRK1: Neurotrophic receptor Tyrosine Kinase-1 Location: Chromosome 1; 1q23.3

NTRK1 encodes a Tropomyosin receptor kinase [Trk]; these tyrosine kinases are membrane-bound and activated by neurotrophins. Some neutrophils which

activate the receptors are Brain-derived neurotrophic factor [BDNF], nerve growth factor [NGF], neurotrophin-3, and neurotrophin-4. Neutrophine signaling results in cell proliferation, survival, the fate of the neural precursor's cell, programmed cell death, *etc* [5]. As the Trk receptors are activated by the neurotrophins, their function independent of the neurotrophins is also reported, which makes them an oncogene. The fusion of the tropomyosin gene with the locus of the extracellular locus of the Trk gene leads to the constitutive expression of the Trk gene, which results in continuous cellular proliferation [6]. Higher expression of the neurotrophins is a clear indication of the progression of cancer and decreases the survival of the patients [7].

1.3. PBX1: Pre-B-Cell Leukemia Transcription Factor-1 Chromosome 1; 1q23.3

PBX1 (Fig. **1**) encodes a protein involved as a transcription factor and belongs to the PBX homeobox family. A fusion protein E2A-PBX1 is produced by the translocation of the t(1;19) (q23.3;p13). This chimeric protein contains transcriptional activation domains from E2A and the homeodomain of PBX1. This complex will disrupt the transcriptional regulation of genes under PBX1 control [8]. Fusion protein E2A-PBX1 has been reportedly associated with pre-B-Cell acute lymphoblastic leukemia. Overexpression of the chimeric protein E2A-PBX1 positive cells in mice has shown hyper-phosphorylation of PLCγ2, which is essential in the proliferation. Its binding has been located to understand the mechanism behind the E2A-PBX1 for enhancing the proliferation using bioinformatics analysis. It has been found that the chimeric protein binds to the kinases located upstream of the PLCγ2 gene, that is, ZAP70, LCK, and SYK. Expression of these kinases helps in the phosphorylation of the PLCγ2 and further its involvement in the proliferation [9]. The E2A-PBX1 fusion protein is also detected in non-small cell lung cancer, shows a standard genetic change, and can be used as a biomarker for the early detection of the disease [10].

1.4. ABL2: Tyrosine Protein Kinase ABL2 Chromosome 1; 1q25.2

ABL2 is a tyrosine-protein kinase that activates the cell's survival, invasion, angiogenesis and growth. ABL2 shows overlapping functions with its family member ABL1. A consistent increase in the expression of ABL2 has been reported in advanced high-grade renal, colorectal, and pancreatic tumors. This shows the direct involvement of the ABL2 in the tumor progression [11 - 13]. Reduced expression of ABL2 in non-small cell lung cancer lines reduced cell growth [14]. In the case of other solid tumors like invasive breast carcinoma, lung squamous cell carcinoma, *etc*., ABL2 showed higher amplification and higher

CHAPTER 2

Chromosome 2

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Abstract: The human chromosome 2 was formed by a head-to-head fusion mutation caused by two chromosomes of our ancestors. The gorilla and chimpanzee contain 48 chromosomes in contrast to 46 chromosomes in humans. Ten million years ago, the two chromosomes of apes underwent telomere-to-telomere fusion that gave rise to human chromosome 2. Apart from the exciting history, the human chromosome 2 is involved in various genetic conditions caused due to chromosomal deletions and duplications, leading to SATB2 (Special AT-rich sequence-binding protein 2)-associated syndrome, MBD5 (Methyl-CpG-binding domain 5)-associated neurodevelopmental disorder, 2q37 deletion syndrome, partial trisomy 2, myelodysplastic syndrome as well as cancer. These mutations cause different human abnormalities, such as craniofacial anomalies, cleft palate, genitourinary tract anomalies, microcephaly, hypotonia, heart defects, anemia, and myeloid malignancies. This chapter discusses 50 genes of human chromosome 2 involved in various cancer types.

Keywords: Cancer, CFLAR, Leukemia, Metastasis, MYCN, RALB, RAS, REL, RHOB, Tumor.

1.1. APOB - APOLIPOPROTEIN B CHROMOSOME 2; 2p24.1

APOB encoding apolipoprotein B is a glycoprotein involved in composing and distributing lipids, and mutations in this gene translate a shortened protein causing hypocholesterolemia and familial hypobetalipoproteinemia [1]. APOB is involved in liver cancer in which the gene is mutated [2]. APOB was inactivated in hepatocellular carcinoma, which correlated to poor prognosis [2]. APOB gene signature was associated with other verified signature genes in hepatocellular carcinoma samples showing that silencing of APOB was related to poor prognosis in hepatocellular carcinoma [2]. Network analysis results showed that the activity

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of low-APOB was linked to increased certain regulators necessary for metastasis and oncogenesis and decreased tumor suppressors compared to high-APOB activity in the progression of hepatocellular carcinoma [2].

1.2. BOLL - BOULE HOMOLOG, RNA BINDING PROTEIN CHROMOSOME 2; 2q33.1

BOLL gene (Fig. **1**) comes under DAZ or Deleted in Azoospermia gene family is the parent gene and plays a role in spermatogenesis [3]. BOLL was involved in colorectal cancer, where the expression of this gene was upregulated [3]. BOLL promoter was more methylated in colorectal cancer tissues than in normal tissues [3]. Also, BOLL was highly expressed in colorectal cancer cell lines, which led to the proliferation and migration of these cancer cells and increased the number of cells in the S-phase of the cell cycle [3]. These observations indicated that BOLL has an oncogenic property with increased promoter methylation, particularly in colorectal cancer [3]. BOLL could be a potential prognostic cancer for colorectal cancer [3].

1.3. BUB1 - BUB1 MITOTIC CHECKPOINT SERINE/THREONINE KINASE CHROMOSOME 2; 2q13

BUB1 is a serine/threonine kinase that plays a role in cell cycle checkpoint in mitosis. It localizes along with other proteins involved in the spindle checkpoint to the kinetochore during chromosome congression [4]. Upregulation of BUB1 led to augmentation of phosphorylation of SMAD2 protein and cell proliferation in liver cancer tissues compared to normal liver tissues suggesting that BUB1 might have the diagnostic potential of liver cancer [5]. The role of BUB1 in glioblastoma was also reported, where it was overexpressed and led to cell proliferation and tumor development *in vivo* and *in vitro* [6]. It also serves as a poor prognostic factor due to its increased expression in patients with glioblastoma [6].

1.4. CCL20 - C-C MOTIF CHEMOKINE LIGAND 20 CHROMOSOME 2; 2q36.3

CCL20 is involved in various types of cancers. The expression of CCL20 was induced by interleukin-1β, which activated signaling pathways in non-small cell lung cancer, where it was upregulated compared to normal samples of lung cells. This resulted in the proliferation and migration of lung cancer cells [7]. CCL20 can serve as a therapeutic target for non-small cell lung cancer [7]. CCL20 was highly expressed in breast cancer patients, which led to reduced survival of these patients [8]. Expression of CCL20 also led to bone metastasis in breast cancer, where it increased the activity of nuclear factors, such as kappa-B and

osteoprotegerin in osteoblastic cells and breast cancer cells and suggest that CCL20 has therapeutic potential in breast cancer bone metastasis [8].

1.5. CFLAR - CASP8 AND FADD-LIKE APOPTOSIS REGULATOR CHROMOSOME 2; 2q33.1

CFLAR, an anti-apoptotic protein homologous to caspase-8 commonly known as c-FLIP or Cellular FLICE-like Inhibitory Protein, plays a major role in inhibiting tumor necrosis factor-α (TNF- α) and TNF-related apoptotic factors and apoptosis during chemotherapy [9]. CFLAR, or c-FLIP, was upregulated in various cancers such as cervical cancer, hepatocellular cancers, head and neck squamous cell carcinoma, and colorectal cancers [9]. c-FLIP also plays a role in non-Hodgkin lymphomas (NHLs), where the expression of c-FLIP could assist in finding the progression of tumors and prognosis of NHLs [10]. c-FLIP inhibits the ligands of death receptors during chemotherapy, causing resistance in cancer cells [10].

1.6. CREB1 - CAMP RESPONSIVE ELEMENT BINDING PROTEIN 1 CHROMOSOME 2; 2q33.3

CREB1 is a transcription factor that controls the proliferation of cells by phosphorylation and dephosphorylation [11], which is targeted by miRNAs in different cancers, such as colorectal, breast, gastric, and ovarian cancer serving as a potential target to treat cancer [12]. miR-122 was one of the miRNAs that targeted CREB1 in bladder cancer in which CREB1 was overexpressed in bladder cancer cell lines and tissues, and miR-122 regulated the expression of *CREB1,* leading to cell invasion and cell proliferation which further could serve as a potential target for bladder cancer [11]. *CREB1,* along with miR-373, was induced by norepinephrine led to colon cancer cell's invasion, proliferation, and metastasis [13].

1.7. CTLA4 - CYTOTOXIC T-LYMPHOCYTE ASSOCIATED PROTEIN 4 CHROMOSOME 2; 2q33.2

CTLA-4 (Fig. **1**) is a glycoprotein that plays a significant role in the immune response. It is expressed on the membranes of T cells to inhibit T cell division and is also involved in the cell cycle and cytokinesis [14]. Expression of CTLA-4 with single nucleotide polymorphisms (SNPs) was observed in various cancers such as melanoma, hepatocellular carcinoma, colorectal cancer, cervical cancer, renal cell carcinoma, *etc* [14]. An SNP in exon 1 of CTLA-4 leads to a threonine-to-alanine (A/G) exchange [15]. When this SNP in breast cancer was compared to normal breast, the incidence of the GG genotype was reduced in patients with breast cancer. Also, the AA genotype was correlated to the tumor size, indicating that CTLA-4 polymorphism promotes tumor formation [15].

CHAPTER 3

Chromosome 3

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Abstract: Myriad genes in the genome have been implicated in cancer. However, a focused compilation of genes from the same chromosome would provide a valuable detailed yet succinct catalog for researchers, advantageous in quickly understanding the leading roles played by these genes in cancer. This chapter fulfills the above aim of furnishing a pocket dictionary- like a concise yet meticulous explanation of many genes from Chromosome 3, describing these genes' functional essentialities in various cancers. Such a judicious collection of genes from a single chromosome is probably the first of its kind. The multiple inputs in this chapter from Chromosome 3 include oncogenes (BCL6, RAF1), tumor suppressor genes (SRGAP3, FHIT), transcription factors (FOXP1, MITF), fusion genes (MECOM), and many other types. With approximately 1085 genes spanning 198 million base pairs, Chromosome 3 constitutes 6.5% of the total DNA.

Keywords: Ductal carcinoma, Glioma, Leukemia, Melanoma, MicroRNA, Neuroblastoma, Oncogene, Oncoprotein, Prostate cancer, Stem cells, Tumorigenesis.

1. INTRODUCTION

Chromosome 3 consists of 198 million base pairs. Hence, chromosome 3 roughly symbolizes 6.5% of the total deoxyribonucleic acid in 1 cell. Chromosome 3 is a metacentric chromosome closely associated with many congenital disabilities including deafness. Let us take a deeper look at some of the genes from Chromosome 3 that have been reported in cancer.

1.1. BCL6: B-Cell Lymphoma 6 Chromosome 3; 3q27.3

After BCL6 discovery in B-cell lymphomas, BCL-6 was widely regarded as an oncogene [1]. The BCL-6 locus undergoes translocations in diffuse large B-cell

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lymphomas [DLBCL] [1]. Such translocations cause the promoter switch of the BCL-6 coding region [1]. BCL6 can initiate tumorigenesis through the suppression of DNA damage checkpoints [1]. BCL6 has been under current scrutiny to consider it a prospective drug target [1]. BCL6 has been reported in solid and hematological cancers [1]. BCL6 gene expression is essential for NSCLC cell survival [1].

1.2. RAF1: Rapidly Accelerated Fibrosarcoma, Chromosome 3; 3p25.2

RAF1 codes for c-RAF (Fig. **1**). RAF1 impacts cellular migratory potentials, cell cycle, apoptosis, and senescence [2]. In the RASRAF- MEK-MAPK cellular signaling pathways, RAF1 has a significant effect [2]. RAF1 can be used as a prognostic marker in NSCLC patient's post-therapy [2]. RAF functions as a cellular oncogene. Even metastasis and invasive potential can be determined from the oncogenic hits in RAF [including RAF1] [2, 3].

1.3. TFG: Tropomyosin-Receptor Kinase Fused Gene Chromosome 3; 3q12.2

TFG fusion proteins have been described to cause tumorigenesis [4]. The function of this TFG protein in cancer has had paradoxical reports; some reports state that TFG could function as a tumor suppressor, while others say that TFG could serve as an oncoprotein [4]. TFG has been implicated in metastatic melanoma with a tumor suppressor function [5]. TFG has been identified as a mutational hotspot that could hold clinical significance for diagnosing and treating metastatic melanoma [5].

1.4. SRGAP3: SLIT-ROBO Rho GTPase-Activating Protein 3 Chromosome 3; 3p25.3

SRGAP3 gene (Fig. **1**) codes for an enzyme that regulates actin and microtubule dynamics [6]. SRGAP3 is a negative modulator of Rac1 [6]. SRGAP3 functions as a tumor suppressor in mammary epithelial cells [6]. SRGAP3 expression is depleted in breast cancer cells [6]. SRGAP3 under expression would promote anchorage-independent growth of breast cancer cells [6]. Lower levels of SRGAP3 expression have been reported in osteosarcomas and invasive breast carcinomas [7].

1.5. GATA2: GATA Binding Protein 2 Chromosome 3; 3q21.3

GATA2 is a crucial endothelial transcription factor that regulates Androgen Receptor [AR] activity [8]. GATA2 has been linked with the progression of prostate cancer in an AR-dependent and independent manner [8]. GATA2 hyper-expression in prostate cancer rapidly augments proliferation, drug resistance, and

metastatic invasion [8]. GATA2 is a prominent factor for the marked aggressiveness in prostate cancer and, henceforth, could be a suitable target for novel drug therapies [8].

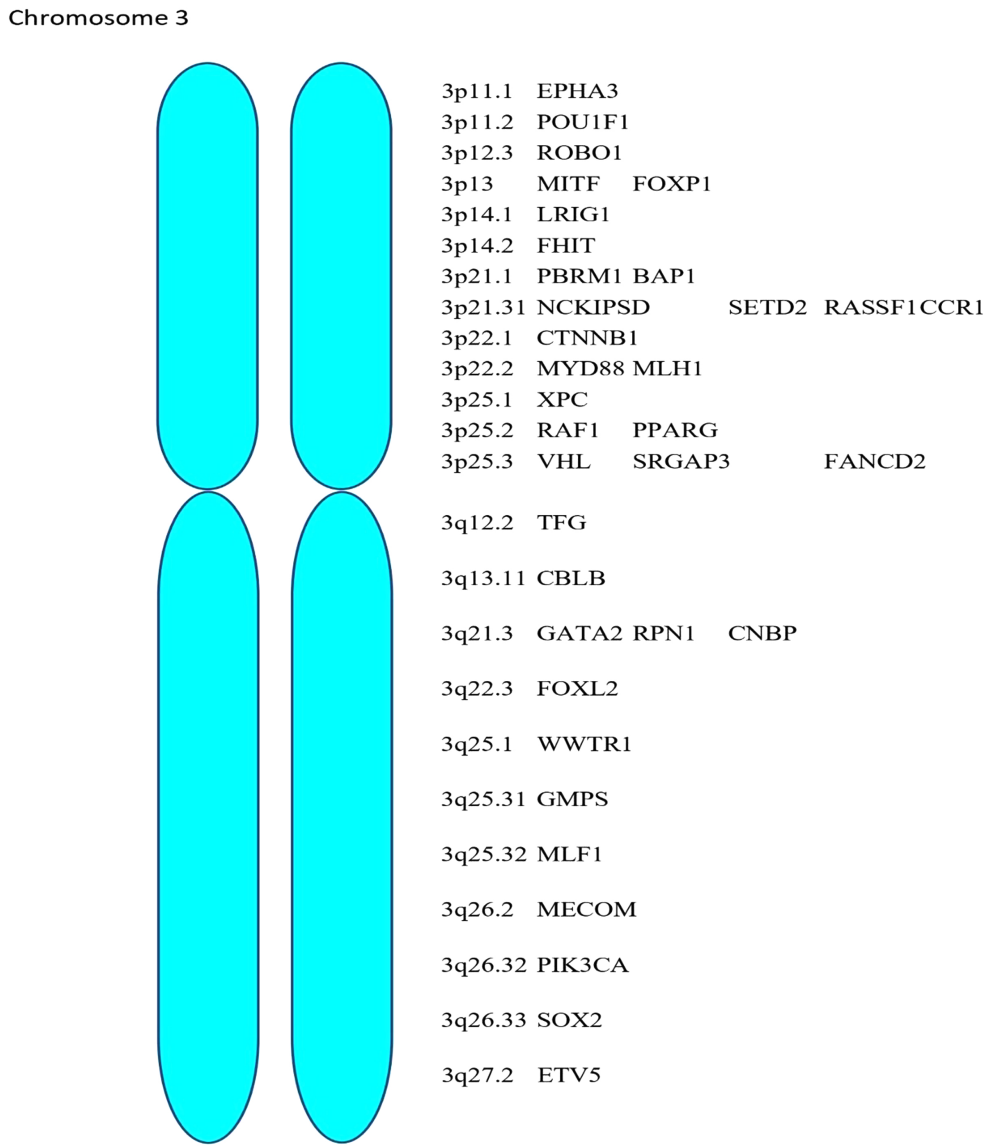

Fig. (1). This figure displays the loci of the genes from Chromosome 3 whose roles in cancer have been explained in this chapter. Sayooj Madhusoodanan designs this diagram.

CHAPTER 4

Chromosome 4

Anindita Menon[1], Ravi Gor[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

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Abstract: Chromosome 4 represents around 6 percent of the total DNA in the cell with 191 million DNA base pairs. Genetic changes in chromosome 4, such as somatic mutation, and chromosomal rearrangement like translocation, gene deletion, *etc*., have been reported to develop several types of cancer. This includes leukemias, multiple myeloma, oesophageal squamous cell carcinoma, prostate cancer, breast cancer, bladder cancer, *etc*. In this chapter, we have listed genes residing in chromosome 4, which further frequently support cancer development, progression, and metastasis.

Keywords: Bladder cancer, Breast cancer, Cancer, Gene deletion, Leukemia, Metastasis, Multiple myeloma, Oesophageal squamous cell carcinoma, Prostate cancer, Somatic mutation, Translocation.

1.1. AAA2 - AORTIC ANEURYSM, FAMILIAL ABDOMINAL 2 CHROMOSOME 4; 4q31

AAA2 is associated with an abdominal aortic aneurysm. ATPase family AAA domain-containing protein 2 (ATAD2) is related to many cellular processes, such as cell proliferation, invasion, and migration. Knocking of this gene in HeLa and SiHa cells showed a reduction in the capacity for invasion and migration and inhibited growth and clonogenic potential in these cell lines [1]. This gene is also a therapeutic target in various tumors, and profiling reveals dysregulation of ATAD2 specifically in Oesophageal Squamous Cell Carcinoma (ESCC). In-vivo experiments showed the suppressive effect of siRNA-mediated ATAD2 silencing on tumor growth in nude mice. Thus, downregulating the gene restrains the malignant phenotype of ESCC through inhibition of the Hedgehog signaling pathway [2].

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1.2. ABCG2- ATP BINDING CASSETTE SUBFAMILY G MEMBER DOMAIN 29 CHROMOSOME 4; 4q34.1

They are a member of the ADAM family and are membrane-anchored proteins that structurally are similar to snake venom disintegrins with implicated biological processes involving cell-cell and cell-matrix interaction, including fertilization, muscle development, and neurogenesis. This protein encodes a gene highly expressed in the testis and is involved in spermatogenesis—alternate splicing results in multiple transcript variants. ADAM29 has been a susceptible locus with risk factors in breast cancer under genome-wide significance. Transcript expression was found more in breast cancer tissue than in normal tissue. They may be a prognostic marker for human breast cancer and a novel therapeutic target [3].

1.3. AFF1- AF4/FMR2 FAMILY MEMBER 1 CHROMOSOME 4; 4Q21.3-q 22.1

This gene (Fig. **1**) encodes a member of the AF4/ lymphoid nuclear protein related to the Fragile X syndrome family of proteins, which have been implicated in human childhood lymphoblastic leukemia, fragile X chromosome, intellectual disability, and ataxia. Members of this family have three conserved domains N-the terminal homology domain, the AF4/ lymphoid nuclear protein domain, and a C- terminal homology domain. The protein regulates RNA polymerase II-mediated transcription through elongation and chromatin remodeling functions. The translocation of genes results in fusion genes. These fusion genes may be due to genetic and environmental factors [4].

1.4. AFP-ALPHA-FETOPROTEIN CHROMOSOME 4; 4q13.3

AFP is a type of plasma protein produced in the yolk sac and the liver during fetal life. AFP expression in adults is associated with hepatocarcinoma and teratoma and has prognostic value for managing advanced gastric cancer. However, hereditary persistence of alpha-fetoprotein is also found, but these individuals show no obvious pathology. The protein is thought to be the fetal counterpart of serum albumin. The AFP and albumin genes are both present in tandem in the same transcriptional orientation on chromosome 4. AFP is found in monomeric, dimeric, and trimeric forms. They also bind to copper, nickel, fatty acids, and bilirubin. The level of AFP in amniotic fluid can be used to measure renal loss of protein to screen spina bifida and anencephaly, which are disorders that are caused due to improper development of neural tubes. DNA methylation of its promoter is the driving mechanism of such overexpression(>400ng/ml). These

tumors show a distinct phenotype characteristic, such as poor differentiation, enrichment of progenitor features and enhanced proliferation [5]. AFP concentration in blood serum is the most specific tumor marker for screening and diagnostic methods [6].

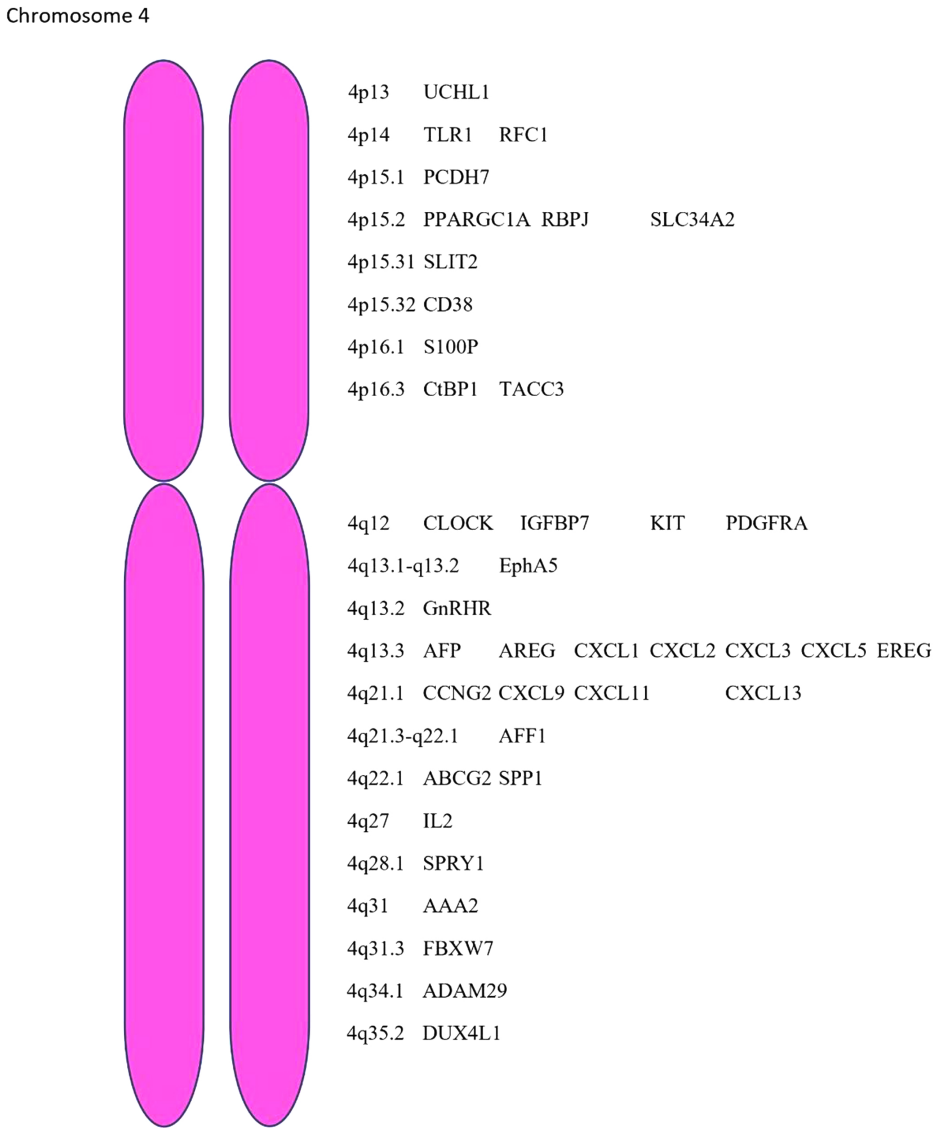

Fig. (1). This figure displays the loci of the genes from Chromosome 4 whose roles in cancer have been explained in this chapter. Sayooj Madhusoodanan designs this diagram.

CHAPTER 5

Chromosome 5

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Abstract: Chromosome 5 presents an extensive collection of genes, and includes several cancer-associated ones. The contribution of chromosome 5 in abnormalities is evident through somatic translocations, germline, somatic, and, in some instances, expression of genes. Various syndromes are associated with chromosome 5, such as 5q minus syndrome, leading to the development of acute myeloid leukemia, PDGFRB-associated chronic eosinophilic leukemia contributing to acute myeloid leukemia, and myelodysplastic syndromes. Studies propose that a few genes on chromosome 5 play important roles withinside the increase and department of cells. When chromosome segments are deleted, as in a few instances of AML and MDS, those crucial genes are missing. Without those genes, cells can develop and divide too speedy and in an out-o--control way. Researchers are trying to perceive the genes on chromosome five that might be associated with AML and MDS.

Keywords: Cellular differentiation, Epigenesis, Follicular variants, Hypermethylation, Intercellular communication, Microsatellite instability, Multi-drug resistance, Polymorphism, Signet-ring cancer, Signal transduction, Translocation.

1.1. AACSP1: ACETOACETYL-COA SYNTHETASE PSUEDOGENE 1. CHROMOSOME 5; 5q35.3

AACSP1 is a pseudogene and is reported to regulate genes similarly to LncRNAs in the human genome. In renal cell carcinoma, alterations in this gene are observed, and this was because LncRNAs and pseudogenes are closely related to survival and recurrence, suggesting they can serve as potential prognostic markers and are worth further investigation [1]. AACSP1 is involved in lipid metabolism and serves as a marker for it. In a study on non-small cell lung carcinoma, it was observed that there is a direct correlation between the changes in the concentrations of lipid metabolites with changes in the expression levels of AACSP [2]. In

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asbestos-related lung cancer, DNA methylation changes were observed in the DNA methylation regions (DMR) in T and N between the asbestos-exposed and non-exposed cases, and AACSP1 showed lowered asbestos-related hypomethylation in lung tumors with asbestos-exposed cases [3].

1.2. ABLIM3: ACTIN BINDING LIM PROTEIN FAMILY MEMBER 3. CHROMOSOME 5; 5q32

ABLIM3 is the third member of the actin-binding LIM protein subgroup. ABLIM3 expression is highest in the heart, lungs, liver (fetal and adult), brain/-cerebellum, CNS, and spinal cord. The expression profile of the abLIM3 gene supports a suggested role in hepatoma development [4]. The knockdown of ABLIM3 resulted in significant impairment of hepatitis C virus replication in HCV- induced hepatocellular carcinoma [5]. The expression of ABLIM3 mRNA is downregulated for triple-negative breast cancer and adjacent non-tumor tissues [6]. Hyper or hypomethylation of ABLIM3 is observed in connection with thyroid cancer. The mutation of ABLIM3 in Kidney renal clear cell carcinoma may play a key role in kidney cancers. The signal transduction and system processes were enriched and interacted between different cancers, reflecting the standard processes in tumor progression and development [7].

1.3. ACOT12: ACYL-COA THIOESTERASE 12. CHROMOSOME 5; 5q14.1

Acyl-CoA thioesterase 12 (ACOT12) is the major enzyme known to hydrolyze acetyl-CoA's thioester bond in the liver cytosol [8]. In a study, it was observed that there is a close association between increased acetyl-CoA levels and hepatocellular carcinoma (HCC) metastasis. Down-regulation of ACOT12 is correlated with metastasis and poor prognosis of HCC. ACOT12 functionally suppresses HCC metastasis. ACOT12 regulates acetyl-CoA metabolism, and histone acetylation down-regulation of ACOT12 promotes HCC metastasis by epigenetic induction of TWIST2 [9]. ACOT12 is linked with growth and invasion potential.

1.4. ACSL6: ACYL-COA SYNTHETASE LONG-CHAIN FAMILY 6. CHROMOSOME 5; 5q31.1

The ACSL6 gene (Fig. **1**), called acyl CoA synthetase 2 (*ACS2*) and fatty acid CoA long chain 6, encodes a long-chain acyl-CoA synthetase. This enzyme is essential in lipid metabolism and cell ATP generation pathways [10]. A study suggests that t(5;12) (q23- 31; p13)/ETV6-ACSL6 gene fusion in chronic

leukemia renders cancer cells resistant to treatment using a tyrosine kinase inhibitor [11]. Another study suggests that the expression of ACSL6 was down-regulated and serves as a potential tumor suppressor gene in leukemia. In addition, ACSL6 was decreased in most forms of cancers, except colorectal cancer [12].

ACSL6 is highly expressed in brain tissue. A bioinformatics study in colorectal cancer found that ACSL6 is upregulated compared to healthy tissue. ACSL6 is speculated to support the accumulation of lipid droplets in fatty liver disease, thereby required for the early stages of hepatocellular carcinoma development [13].

1.5. ACTBL2: ACTIN BETA LIKE 2 [HOMO AAPIENS (HUMAN)]. CHROMOSOME 5; 5q11.2

Actin beta-like 2 (ACTBL2) was found to have higher levels in colorectal tumor samples, indicating ACTBL2 association and differential upregulation in colorectal cancer, thereby potentially serving a function in developing markers for colorectal cancer [14]. A study found that increased expression of ACTBL2 was observed in human pancreatic ductal adenocarcinoma [15]. In a survey of human breast cancer cell lines, ACTBL2 was one of the top ten genes to be upregulated [16]. ACTBL2 is a cytoskeletal protein abundantly expressed in vascular smooth muscle cells. ACTBL2 was most strongly associated with epithelial ovarian cancer risk [17]. ACTBL2 is found to differentiate between conventional and follicular variants of papillary thyroid cancer [18].

1.6. ACTBP2: ACTB PSEUDOGENE 2 [HOMO SAPIENS (HUMAN)]. CHROMOSOME 5; 5q14.1

The ACTBP2 locus (Fig. **1**) consisting of AAAG repeats on human chromosome 5 is one of the most polymorphic short tandem repeat systems [19]. ACTBP2 is used as a marker in studying microsatellite instability in cancer cells [20]. In a study on ovarian cancer, the microsatellite instability at the ACTBP2 locus is found in 20% of the cancers [21]. ACTBP2 can be used as a microsatellite repeat marker to assess patients with bladder cancer using a non-invasive technique and thereby can be used as a potential biomarker for bladder cancer patients [22]. Knowing the sensitivity of ACTBP2 in bladder tumors, it was used to detect non-small cell lung cancers (NSCLC), detecting an alteration in primary lung tumors. Hence, markers sensitive to NSCLC may also be used for detecting tumors from other organs [23]. A study detected loss of heterozygosity at the ACTBP2 locus in the plasma of small-cell lung cancer patients [24]. ACTBP2 shows a high rate of

CHAPTER 6

Chromosome 6

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Abstract: Chromosome 6 is among the 23 pairs of chromosomes in humans and it spans about 170 million base pairs. Several cancer genes have been identified to have a role in cancer development. Cancer is also a genetic disease caused due to changes in the genes that control cell function, such as cell division and cell growth. Most of these cancer genes either act as tumor suppressors or possess an oncogenic potential. Oncogenes like ROS1, MYB, HMGA1, *etc*., induce tumorigenesis by playing a role in DNA repair, replication, transcriptional regulation, and mRNA splicing. When these genes are highly expressed, they result in the transformation of normal cells to malignant cells; on the other side, tumor suppressor genes like IGF2R, AIM1, IRF4, *etc*., reduce tumorigenicity and invasive potential. Thus, reduced expression of these genes due to loss of heterozygosity, deletion or any epigenetic modifications can induce tumor formation. Also, some genes can either suppress or induce tumor formation given the cellular location and condition, such as CCN2, TNF, *etc*. Along with these, different types of structural abnormalities can be observed on chromosome 6, such as chromosomal translocation, deletion, duplication, and inversion. These abnormalities on both p and q arms have been known to contribute to the growth and spread of cancer by impacting the expression of cancer genes. Aberrant expression of the genes can also be influenced by fusions, missense mutations, non-missense mutations, silent mutations, frame-shift deletions, and insertion at the molecular level. Some genes can maintain stem-cell-like properties by regulating the expression of cell surface markers like Oct4, Nanog, Sox4, *etc*. This chapter explains important cancer genes, genetic mutations, and gene variations that can influence the risk of having cancer and induces cancer formation.

Keywords: A Cancer stem cell, Chromosome 6, Chromosomal translocation, Deletion, Oncogenes, Tumor suppressor genes.

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1.1. GENE- AFDN; AF-6; AFADIN, ADHERENS JUNCTION FORMATION FACTOR LOCATION: 6p27

AFDN gene (Fig. **1**) encodes a multi-domain protein that plays a key role in the organization of epithelial structures of the embryonic ectoderm and is also involved in the signaling and organization of cell junctions during embryogenesis. Aberrant expression of the *AFDN* gene has been shown to induce epithelial-to-mesenchymal [EMT] transition leading to cell migration, invasion, and proliferation in cancer, such as breast cancer, colon cancer, and pancreatic cancer.

Low expression of *AFDN* has been associated with many types of tumors, such as osteosarcoma, breast cancer, and gastric cancer.

1.1.1. The Disease of Relevance

- *AFDN* gene is involved in chromosomal translocation [6, 11][q27;q23] in the case of acute myeloid leukemia [AML] by forming a fusion partner with the acute lymphoblastic leukemia [*ALL-1*] gene. This self-association of the protein afadin activates the oncogenic potential of the MLL-afadin fusion protein. Maintaining the expression on *MLL-AFDN* [*AF6*] driven oncogenic gene expression requires the continuous activity of the histone-methyltransferase DOT1L [1, 2].
- In breast cancer, phosphorylation of afadin by the Akt signaling pathway at Ser1718 promotes the relocalization of afadin from the adherens junction to the nucleus, which further results in breast epithelial cell migration. This relocalization can also occur due to the presence of wild-type or Ser1718Asp mutant afadin that is nuclear restricted and also enhances cell migration. Increased metastatic relapse in breast carcinoma is associated with afadin low expression [3, 4].
- Silencing of *AFDN* expression is known to reactivate the ERK signaling pathway, and this interaction promotes the metastasis phenotype in osteosarcoma cells by stably expressing claudin-2 [*CLDN2*]. Reduced expression of *CLDN2* and *AFDN* are found to participate in pulmonary metastasis of OS and thus can be used as a potential molecular marker for the diagnosis of OS and can also help to determine the prognosis [5].
- Downregulation of long non-coding RNA [lncRNA] MLLT4-AS1 is significantly associated with lymph node metastasis, distant metastasis, and a shorter disease-free interval in Gastric Cancer. Thus in this cancer, it acts as a tumor suppresser gene, and down-regulation of *MLLT4-AS1* is a potential marker of a poor prognosis. Few studies have shown that infection with *H.pylori* can reduce the expression of afadin, leading to cell migration [6, 7].
- In colon cancer, *AFDN* or afadin physically interacts with Cystic fibrosis

transmembrane conductance regulator [*CFTR*] at a cell to cell contacts, so knockdown of *CFTR* results in reduced stability of afadin protein and enhanced malignancies [8].

- Reduced expression of *AFDN* induces transcription of Snail, which is an EMT inducer, thus promoting *tumorigenesis* in human pancreatic adenocarcinoma [9].
- Loss of *AFDN* expression results in myometrial invasion and high histological grade in patients with `uterine corpus endometrial carcinoma. It is known to induce chemoresistance to cisplatin and so can be used as a marker of chemo-resistance to cisplatin [10].

1.2. GENE- DEK; DEK PROTO-ONCOGENE LOCATION: 6p22.3

DEK gene (Fig. **1**) codes for nuclear protein, and its expression has been linked to numerous cancer occurring through multiple mechanisms. It is involved in DNA repair, replication, transcriptional regulation, and mRNA splicing, so any changes in the gene expression can lead to tumorigenesis. *DEK* overexpression has been reported in several malignancies like leukemia, melanoma, hepatocellular carcinoma, malignant brain tumors, uterine cervical cancer, lung cancer, glioblastoma, urinary bladder cancer, ovarian cancer, and most sarcoma cell carcinoma. The resequence project of the cancer genome has shown a heterozygous missense mutation [K348N] of *DEK* in the case of renal tumors.

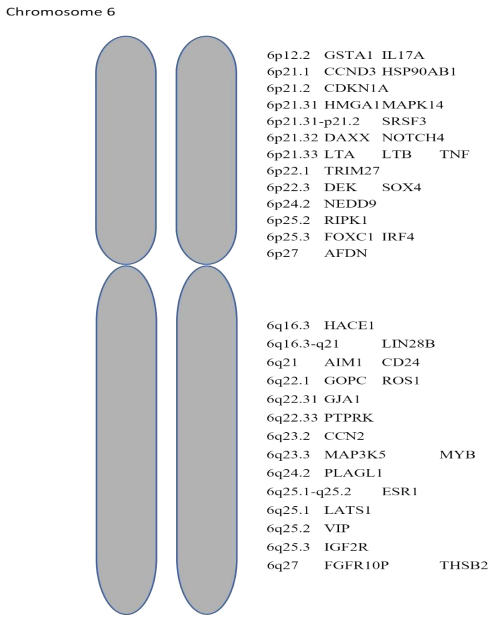

Fig. (1). This figure displays the loci of the genes from Chromosome 6 whose roles in cancer have been explained in this chapter. Sayooj Madhusoodanan designed this diagram.

CHAPTER 7

Chromosome 7

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Abstract: Chromosome 7 consists of 159 million base pairs, and around 950 genes, representing at least 5 percent of the entire DNA in a cell. Various genes that regulate cell division and cellular growth are present in Chromosome 7. Aberrations in these genes can therefore lead to tumorigenesis. Lymphomas and Leukemia have been frequently correlated with abnormalities on chromosome 7. Aberrations in chromosome 7, such as aneusomy in prostate cancer, gene amplifications in gastric cancer, and chromosomal gain in glioblastoma, are some of the starkly real ramifications of genetic abnormalities on chromosome 7. Numerous essential genes from Chromosome 7, including ABCB5, BRAF, CDK6, EGFR, ETV1, EZH2, IL6, and TWIST1, involved in cancer have been explained in this chapter.

Keywords: Liver cancer, Breast cancer, Colorectal cancer, Esophageal cancer, Gastric cancer, Leukemia, Lymphoma, Melanoma, Ovarian cancer, Pancreatic cancer, Prostate cancer, Renal cancer.

1.1. ABCB5 - ATP BINDING CASSETTE SUBFAMILY B MEMBER 5 LOCATION: CHROMOSOME 7; 7p21.1

This gene encodes for a member of the ATP-binding cassette [ABC] transporter superfamily of integral membrane proteins. These proteins participate in ATP-dependent transmembrane transport of structurally diverse molecules, ranging from small ions, sugars, and peptides to more complex organic molecules [1]. This ABCB5 protein is said to promote the invasiveness and metastasis of cancer cells in both breast and colorectal cancer [2, 3]. This protein has also been proven to regulate a Pro-Inflammatory Cytokine Signalling Circuit and thereby maintain melanoma-initiating cells [4].

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1.2. ACTB – ACTIN BETA LOCATION: CHROMOSOME 7; 7p22.1

This gene encodes one of six different actin proteins. Actins are highly conserved proteins involved in cell motility, structure, integrity, and intercellular signaling [5]. The ACTB protein has been used as a reference gene to measure the expression levels of many tumors. Abnormal expression of ACTB has also been reported in liver, melanoma, renal, colorectal, gastric, pancreatic, esophageal, lung, breast, prostate, ovarian cancers, leukemia and lymphoma. These abnormal levels of ACTB are said to improve the invasiveness of tumors and help in cancer metastasis [6 - 8].

1.3. AGR2 - ANTERIOR GRADIENT 2 LOCATION: CHROMOSOME 7; 7p21.1

This gene encodes a member of the disulfide isomerase [PDI] family of endoplasmic reticulum [ER] proteins that catalyze protein folding and thiol-disulfide interchange reactions. This protein plays a role in cell migration, cellular transformation, and metastasis and is a p53 inhibitor [9]. As a p53 inhibitor, ARG2 has been implicated in many cancers, including breast and non-small lung cancer, as a metastasis promoter [10 - 12].

1.4. AKAP9 - A-KINASE ANCHORING PROTEIN 9 LOCATION: CHROMOSOME 7; 7q21.2

The A-kinase anchor proteins [AKAPs] are a group of structurally diverse proteins with the everyday function of binding to the regulatory subunit of protein kinase A [PKA] and confining the holoenzyme to discrete locations within the cell. This gene encodes a member of the AKAP family [13]. AKAP9 proteins have been implicated in thyroid, colorectal, gastric, and breast cancer [14]. The gene resulting from the fusion of AKAP9 and BRAF has been said to activate thyroid cancer by manipulating the MAPK pathway [15].

1.5. AMPH – AMPHIPHYSIN LOCATION: CHROMOSOME 7; 7p14.1

This gene encodes a protein associated with the cytoplasmic surface of synaptic vesicles [16]. APMH is also a critical protein for breast cancer progression [17]. It is also said to manipulate the Ras-Raf-MEK-ERK signal pathway and originally acted as a tumor suppressor for non-small cell lung cancer. Still, mutations in the gene can help activate cancer [18].

1.6. AQP1 - AQUAPORIN 1 LOCATION: CHROMOSOME 7; 7p14.3

This gene encodes a small integral membrane protein with six bilayer-spanning domains that function as a water channel protein. This protein permits passive

water transport along an osmotic gradient [19]. AQP1 is said to be overexpressed in both lung cancers and a particular subgroup of basal-like breast cancers [20, 21]. It was also observed that when AQP1 was knocked down in human ovarian cancer cells, it inhibited their growth and invasiveness [22].

1.7. BRAF - B-RAF PROTO-ONCOGENE, SERINE/THREONINE KINASE LOCATION: CHROMOSOME 7; 7q34

This gene encodes a protein belonging to the RAF family of serine/threonine protein kinases. This protein regulates the MAP kinase/ERK signaling pathway, which affects cell division, differentiation, and secretion [23]. The BRAF protein regulates the Ras-Raf-MEK-ERK signal pathway. Therefore, mutations in this gene lead to the progression of multiple cancer types [24]. Multiple cancer progression resulting from the fusion of AKAP9 and BRAF has been said to activate thyroid cancer by manipulating the MAPK pathway [15, 25].

1.8. CARD11 - CASPASE RECRUITMENT DOMAIN FAMILY MEMBER 11 LOCATION: CHROMOSOME 7; 7p22.2

The protein encoded by this gene (Fig. **1**) belongs to the membrane-associated guanylate kinase [MAGUK] family, a class of proteins that functions as molecular scaffolds for the assembly of multiprotein complexes at specialized regions of the plasma membrane [26]. Mutations in the CARD11 gene are responsible for the progression of Cutaneous Squamous Cell Carcinoma [27]. CARD11 has also been associated with Human Diffuse Large B Cell Lymphoma [28].

1.9. CCM2 - CCM2 SCAFFOLD PROTEIN LOCATION: CHROMOSOME 7; 7p13

This gene (Fig. **1**) encodes a scaffold protein that functions in the stress-activated p38 Mitogen-activated protein kinase [MAPK] signaling cascade. The protein interacts with SMAD-specific E3 ubiquitin-protein ligase 1 [also known as SMUR-F1] *via* a phosphotyrosine binding domain to promote RhoA degradation.

The protein is required for endothelial cell's normal cytoskeletal structure, cell-cell interactions, and lumen formation [29]. CCM2 has been implicated in the tumorigenesis of many cancers.

It is also hypothesized that the CCM2 protein can be a biomarker for various cancers [30].

CHAPTER 8

Chromosome 8

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Abstract: Chromosome 8 spans more than 146 million DNA base pairs, and represents between 4.5 and 5 percent of the total DNA in cells. Sixteen percent of these genes and their mutations have been identified to play a role in cancer development. Cancer is a genetic disease at the somatic cell level. Multiple gene mutations usually precede them throughout one's life. Oncogenes such as Myc, Lyn, Atad2, *etc*., from chromosome 8 promoted cancer cell proliferation, invasion, and migration. The increased expression of these proteins can transform a normal cell into a cancer cell. Chromosome 8 also houses multiple tumor suppressor genes, such as Dlc1, E2f5, Gata4, Ido1, *etc*. These proteins, when expressed, reduce the chances of tumor initiation within cells. Thus, mutations leading to the reduced expression of these genes are associated with multiple cancers. Mutation of other functional genes like Ank1, Ctsb, Ext1, Il7, *etc*., has also been implicated in various cancers for their role in increasing the invasive nature of cancers by regulating angiogenesis and facilitating cancer metastasis. Cancers can also stem from the translocational mutations of genes in chromosome 8. This chapter explains essential cancer genes, genetic mutations, and gene variations that can cause an increased risk of cancer and its progression.

Keywords: A Cancer stem cell, Chromosome 6, Deletion, Gene Mutations, Oncogenes, Tumor suppressor genes.

1.1. ADAM28: ADAM METALLOPEPTIDASE DOMAIN 28 CHROMOSOME 8; 8p21.2

This gene encodes a member of the ADAM (a disintegrin and metalloprotease domain) family. Members of this family are membrane-anchored proteins structurally related to snake venom disintegrins and have been implicated in various biological processes involving cell-cell and cell-matrix interactions, including fertilization, muscle development, and neurogenesis [1]. ADAM28 is

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overexpressed in non-small cell lung carcinomas and has also been proven to correlate with cancer cell proliferation and lymph node metastasis [2].

ADAM28 has also been associated with the proliferation of human breast carcinoma cells through the cleavage of insulin-like growth factor binding protein-3 [3].

1.2. ADAM32: ADAM METALLOPEPTIDASE DOMAIN 32 CHROMOSOME 8; 8p11.22

This gene encodes a member of the disintegrin family of membrane-anchored proteins that play a role in diverse biological processes, such as brain development, fertilization, tumor development, and inflammation. This gene is predominantly expressed in the testis. The encoded protein undergoes proteolytic processing to generate a mature polypeptide comprised of a metalloprotease, disintegrin, and epidermal growth factor-like domains [4]. ADAM32 has been suspected of having a role in multiple carcinomas for its ectodomain-shedding activity of several proteins like Tumour necrosis factor (TNF)-α [5]. GNMTF predictions have also shown that ADAM32 can act as a driver gene for cancer cell proliferation [6].

1.3. ADAM7: ADAM METALLOPEPTIDASE DOMAIN 7 CHROMOSOME 8; 8p21.2

This gene encodes a member of the ADAMs family of zinc proteases. These transmembrane proteins play roles in multiple processes, including cell signaling, adhesion, and migration. The encoded protein lacks protease activity and may play roles in protein-protein interactions and cell adhesion processes, including sperm-egg fusion [7]. Mutations in the ADAM7 gene have been associated with the development of melanomas [8]. It has also been identified as one of 7 biomarker genes in high-risk prostate cancer [9].

1.4. ADAM9: ADAM METALLOPEPTIDASE DOMAIN 9 CHROMOSOME 8; 8p11.22

This gene encodes a member of the ADAM [a disintegrin and metalloprotease domain] family. Members of this family are membrane-anchored proteins structurally related to snake venom disintegrins and have been implicated in various biological processes involving cell-cell and cell-matrix interactions, including fertilization, muscle development, and neurogenesis [10]. Elevated

ADAM9 expression has been detected during the transition of human LNCaP prostate cancer cells from an androgen-dependent to an androgen-independent and metastatic state [11] and *In vivo* targeting of ADAM9 gene expression using lentivirus-delivered shRNA has been shown to suppress prostate cancer growth [12]. ADAM9 has also been shown to be highly expressed in pancreatic cancer [13], human breast cancer [14], and renal cell cancer [15].

1.5. ADGRB1: ADHESION G PROTEIN-COUPLED RECEPTOR B1 CHROMOSOME 8; 8q24.3

ADGRB1, also known as BAI1 (Brain-specific Angiogenesis Inhibitor), contains at least one 'functional' p53-binding site within an intron, and its expression is induced by wildtype p53. There are two other brain-specific angiogenesis inhibitor genes, designated BAI2 and BAI3, which, along with BAI1, have similar tissue specificities and structures; however, only BAI1 is transcriptionally regulated by p53. BAI1 is postulated to be a member of the secretin receptor family, an inhibitor of angiogenesis, and a growth suppressor of glioblastomas [16]. ADGRB1 prevents the formation of Medulloblastomas by protecting p53 from mdm2-mediated degradation [17]. It has also been implicated to have in hepatocellular carcinoma [18]

1.6. ADHFE1: ALCOHOL DEHYDROGENASE IRON CONTAINING 1 CHROMOSOME 8; 8q13.1

The ADHFE1 gene encodes hydroxy acid-oxoacid transhydrogenase [EC 1.1.99.24], which is responsible for the oxidation of 4-hydroxybutyrate in mammalian tissues [19]. ADHFE1 is a breast cancer oncogene and promotes orthotopic tumor growth [20]. It has also been found that the hyper-methylation of the ADHFE1 gene can cause colorectal cancer [21 - 23].

1.7. AGO2: ARGONAUTE RISC CATALYTIC COMPONENT 2 CHROMOSOME 8; 8q24.3

This gene encodes a member of the Argonaute family of proteins which play a role in RNA interference. The encoded protein is fundamental and contains aAZ and PIWI domains. It may interact with dicer1 and play a role in short-interfering-RNA-mediated gene silencing. Multiple transcript variants encoding different isoforms have been found for this gene [24]. The AGO2 gene has a high incidence of gene alterations across cancer types, including invasive breast carcinoma [23.30%], colon and rectum adenocarcinoma [12.3%], bladder

CHAPTER 9

Chromosome 9

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Abstract: Chromosome 9 represents approximately 4.5 percent of the total DNA in cells, and it's a submetacentric type of chromosome. Chromosomal abnormalities in chromosome 9 have been reported in different kinds of cancer, for example, deletion of the long-q arm, a fusion of ABL1 with BCR results in the ABL1-BCR fusion gene, *etc*. Bladder cancer, chronic myeloid leukemia, *etc*., are several cancer types resulting from genetic changes in the genes present in chromosome 9. Dysregulation of the tumor suppressor genes or activation of the oncogene from chromosome 9 has supported the normal cell's transformation. Here, we have listed a few top genes reappearing themselves as causative agent for cancer development in cancer and types of cancer.

Keywords: ABL1-BCR, Bladder Cancer, Chromosomal Abnormalities, Chronic Myeloid Leukemia, Fusion Gene, Genetic Change, Oncogene, q-arm, Submetacentric, Tumor Suppressor.

1.1. ABCA1 - ATP-BINDING CASSETTE, SUBFAMILY A, MEMBER 1 CHROMOSOME 9; 9q31.1

ABCA1 belongs to the ATP-binding cassette transporter (ABC) superfamily [1]. It is involved in the reverse transport of the cholesterol pathway, which helps translocate the phospholipids and cholesterol from the cytoplasm to the cell surface embedded with apolipoproteins and monitors the pathway [1]. Several mutations in this gene lead to a high-density lipoprotein deficiency disorder called Tangier disease, which further causes atherosclerosis [1]. Disruptions in *ABCA1* expression cause cancer and tumor progression [2]. A study observed the correlation between ABCA1 and cholesterol in colorectal cancer where the upregulation of ABCA1 resulted in cell invasion, cell proliferation, and Epithe-

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# Equal authorship and equal contribution status.

lial-Mesenchymal transition away from the primary location [2]. In addition, ABCA1 might induce metastasis and growth of tumors [2]. *ABCA1* gene expression might be a potential biomarker for the prognosis of colorectal cancer [2].

1.2. ANXA1 - ANNEXIN A1 CHROMOSOME 9; 9q21.13

ANXA1 belongs to the superfamily of annexin proteins which binds to phospholipids on cell membranes involving physiological functions such as cellular differentiation, membrane trafficking, proliferation, and signal transduction [3]. In addition, expression of ANXA1 is reported in various cancers, including bladder, liver, lung, skin, prostate, pancreatic, colorectal, endometrial, esophageal, melanoma, cervical cancer, and oral cancer [4]. In prostate cancer, ANXA1 was downregulated under hypoxic conditions resulting in cell invasion and metastasis of the prostate cancer cell line, indicating that ANXA1 might be a useful therapeutic marker for prostate cancer undergoing metastasis [5]. In colorectal cancer, the expression of ANXA1 was increased, leading to early metastasis of lymph nodes and invasion, suggesting that ANXA1 could serve as a biomarker for colorectal cancer prognosis [4].

1.3. AQP3 - AQUAPORIN 3 CHROMOSOME 9; 9p13.3

AQP3 is a water channel protein belonging to the aquaporin protein family that regulates the influx and efflux of water in cells [6]. This protein is expressed in the membrane of chorions in the amniotic fluid and placenta in humans to maintain amniotic fluid homeostasis [6]. Apart from water homeostasis, AQP3 also regulates the flow of solutes of neutral charges, such as urea and glycerol [6]. AQP3 is expressed in normal tissues like the brain, lungs, pancreas, prostate, epithelial cells, breast, liver, ovary, and bladder [7]. Moreover, the expression of AQP3 is increased in pancreatic, colon, hepatocellular carcinoma, and lung cancer [7]. This protein induces proliferation, migration, and invasion of cancer cells, and promotes epithelial-mesenchymal transition [7].

1.4. BAG1 - BCL2- ASSOCIATED ANTHANOGENE 1 CHROMOSOME 9; 9p13.3

BCL2- associated anthanogene 1 (*BAG1*) is widely involved in the development, progression, and metastasis of cancer; overexpression of BCL2- associated anthanogene 1 (BAG1) is reported in breast cancer, it consists of the development of lesions, tumor development, cancer progression, and metastasis [8].

1.5. BRINP1 - BONE MORPHOGENETIC PROTEIN/RETINOIC ACID-INDUCIBLE NEURAL-SPECIFIC PROTEIN 1 CHROMOSOME 9; 9q33.1

This gene is commonly known as Deleted in Bladder Cancer Chromosome 1 (*DBCC1*), which is widely seen in patients with Bladder and Lung cancer, and the effect of this gene is seen lesser in the early stages of lung cancer; this gene is further silenced so that proliferation, migration, invasion of the cancer cells can be controlled, and Lung cancer can be reduced and prevented. Downregulation of Deleted in Bladder Cancer Chromosome 1 (*DBCC1*) is done by DNA methylation [9].

1.6. CA9 - CARBONIC ANHYDRASE 9 CHROMOSOME 9; 9p13.3

Acid transport is significant in cancer cell progression, transport metabolons, cancer invasion, and cell migration; an acid vehicle is seen between bicarbonate and Carbonic anhydrase (*CA9*), which alters the pH, acid, and bases level, which leads to the progression of cancer [10].

1.7. CCL19 - C-C MOTIF CHEMOKINE LIGAND 19 CHROMOSOME 9; 9p13.3

CCL19 is associated with cervical cancer and is also involved in epithelial to mesenchymal transition cervical cancer. The overexpression of the C-C motif ligand 19 (CCL19) leads to the progression of cervical cancer and is also abnormally expressed, which involves tumor development [11].

1.8. CCL21 - C-C MOTIF CHEMOKINE LIGAND 21 CHROMOSOME 9; 9p13.3

CCL21 is expressed during the formation of lymphoid organs and vessels, interacting with glycosaminoglycans and embedding the proteins on endothelial cell surfaces [12]. The CCL21 induces breast cancer proliferation, and this ligand is responsible for the metastasis and progression of tumors in the breast cells and tissues [12].

1.9. CD274 - MOLECULE PROGRAMMED CELL DEATH 1 LIGAND 1 CHROMOSOME 9; 9p24.1

CD274 is also known as PD-1 or Programmed death 1, which regulates the suppression of the immune response to Th1 cytotoxicity *via* negative feedback [12]. This protein is also involved in various cancer, such as Hodgkin's

CHAPTER 10

Chromosome 10

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Abstract: Chromosome 10 contains various genes that are significantly involved in tumorigenesis. These genes described herein that play roles in cancer comprise receptor tyrosine kinases (FGFR2), proto-oncogenes (FRAT1, RET), tumor suppressor genes (PTEN, KLF6), and also genes involved in signal transduction (MAPK8), gene fusions (CCDC6, KIF5B, VTI1A), developmental processes (GATA3, NODAL), Epithelial-Mesenchymal transition (ZEB1, VIM) and epigenetic regulation (MLLT10). This chapter provides a compilation of many such genes from Chromosome 10 that are associated with cancer, with vivid delineations of the underlying molecular mechanisms of each gene in its contribution to cancer initiation, progression and metastasis. Genes that are insufficiently investigated but implicated in tumorigenesis have also been described in this chapter.

Keywords: Apoptosis, Cell Cycle, Cytogenetic Location, Deletion, Down-regulation, Gene, Gene Amplification, Invasion, Malignant, Migration, Mutation, Signal Transduction, Translocation, Tumor Progression, Upregulation.

1.1. ALL1 – ACUTE LYMPHOCYTIC LEUKEMIA LOCATION: CHROMOSOME 10; 10q21

ALL1 protein has been reported in Leukemia. ALL1 gene undergoes translocation with chromosomal band 11q23 [1]. Mutations in this gene have been reported in 5- 10% of Acute Leukemia [1]. ALL gene fusion with chromosome 11 has been reported in 11% of adult *de novo* AML [Acute myeloid leukemia] [2]. ALL1 gene mutation and Trisomy 11 have been frequently correlated in multiple adult AML patients. ALL1 gene undergoes partial tandem duplication of an internal position of itself, thereby triggering leukemogenesis [2]. Various types of self-fusions and tandem duplications among exons of ALL genes have been observed in AML [3]. Such self-fusions and tandem duplication among the exons of the ALL1 gene contribute to genetic instability leading to leukemia [2, 3].

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1.2. ALOX5 - ARACHIDONATE 5-LIPOXYGENASE LOCATION: CHROMOSOME 10; 10q11.21

ALOX5 gene (Fig. **1**) is off 71.9-kilo base pairs. The gene consists of 14 exons and 13 introns. The ALOX5 protein is of 673 amino acids and has a molecular weight of 78 kilo-dalton. Cells involved in inflammatory responses and allergy express ALOX5 [4]. Such cells include neutrophils, basophils, mast cells, and eosinophils [4]. ALOX5 gene dysregulation has been reported in Chronic Myeloid Leukemia [CML] [5]. ALOX5 is a critical regulator of Cancer Stem Cells [CSC] in CML [5]. ALOX5 promotes the activity of Leukemia Stem Cells in CML [5]. ALOX5 deficiency failed BCR-ABL to induce leukemogenesis in CML [5]. Neutrophils support lung metastasis of breast cancer *via* ALOX5-dependent leukotriene release [4]. Inhibition of ALOX5 using Zileuton inhibited breast cancer's lung metastasis and the activity of Leukemia Stem Cells in CML [4, 5]. Contrary to the theory that ALOX5 is a novel target against CSC, it was further reported that deletion of ALOX5 in the tumor microenvironment could aggravate lung cancer progression [6] since ALOX5 gene products had antitumor roles in the tumor microenvironment *via* T-cell recruitment [6]. Hence, recent research suggests that caution must be taken while targeting ALOX5 though it provides a novel target against CSC [5, 6].

1.3. CAMK1D- CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE ID ` LOCATION: CHROMOSOME 10; 10p13

CAMK1D belongs to the CaMK family of Ca2þ/calmodulin-regulated serine/ threonine protein kinases [7]. CAMK1D gene is amplified and overexpressed in most breast cancers [7]. CAMK1D overexpression in non-tumorigenic breast epithelial cells indicated EMT [Epithelial Mesenchymal Transition]. CAMK1D is reported to be the driver oncogene in multiple basal-like tumors. CAMK1D is identified to be a novel oncogene that promotes EMT in breast cancer and could be used as a potential therapeutic target for basal-like tumors [7]. CAMK1D is essential for cellular proliferation [7 - 9]. CAMK1D has been shown to promote fibroblast proliferation by activating the cyclin D- 1/CDK4 complex [7, 8]. It's yet to be found if CAMK1D enhances proliferation through the exact mechanism in other cell types. Nevertheless, CAMK1D is associated with CREB pathway activation in basal breast cancers [7]. It's yet to be speculated if CREB protein is a direct target of CAMK1D or if CAMK1D associates with genes containing CREB sequence [7, 8, 10]. Such an example is the CCND1 gene that codes for Cyclin D-1 and contains a CREB sequence in its promoter region [7, 10]. CAMK1D is a new potential target for molecular-targeted therapy since CAMK1D promotes

EMT, which is vital to invasion and metastasis, adding to the fact that kinases have always been used as previous drug targets [7].

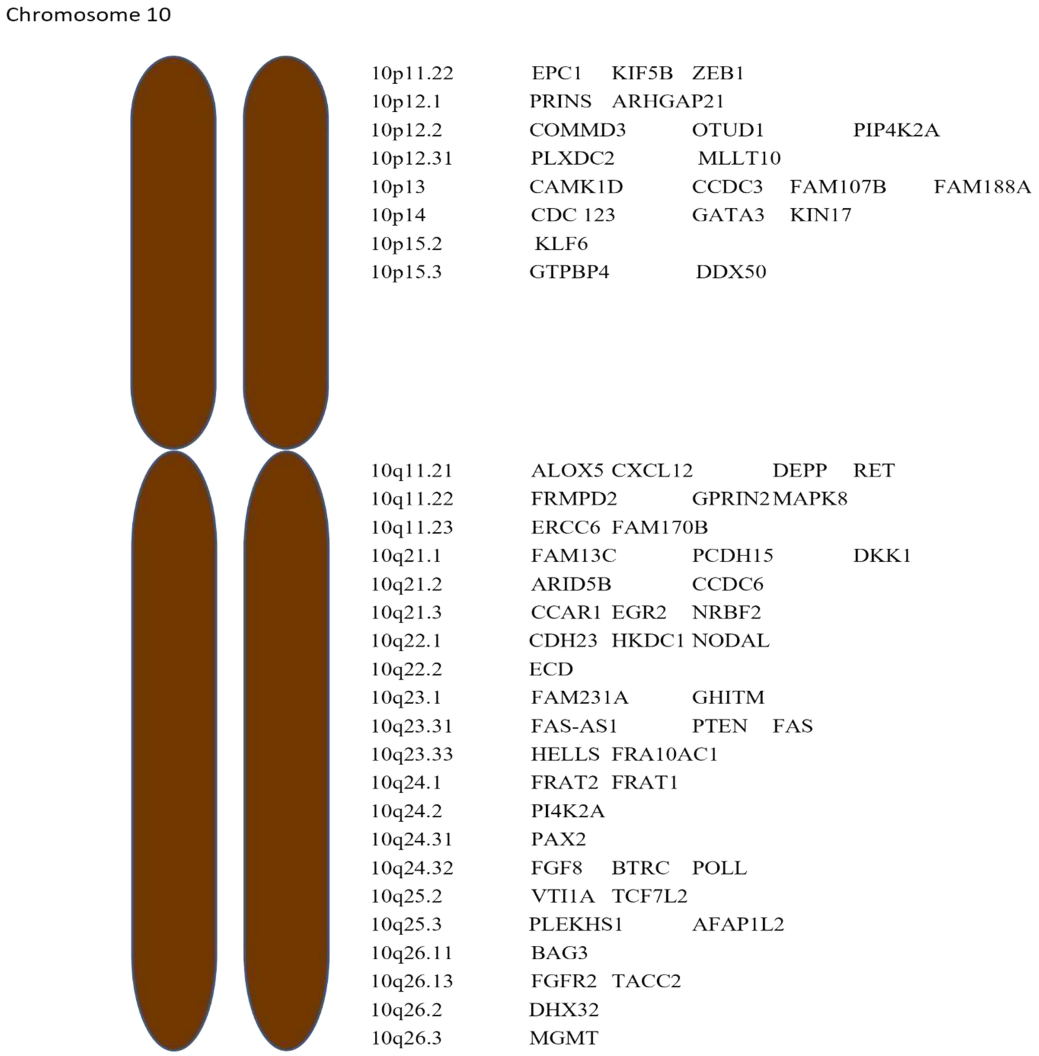

Fig. (1). This figure displays the loci of the genes from Chromosome 10 whose roles in cancer have been explained in this chapter. Sayooj Madhusoodanan designed this diagram.

1.4. ARID5B: AT-RICH INTERACTION DOMAIN 5B LOCATION: CHROMOSOME 10; 10q21.2

ARID5B gene mutations have been reported in childhood acute lymphoblastic leukemia [ALL] [11]. ALL is the most common malignancy reported in childhood [12]. Genome-Wide Association Studies [GWAS] have exposed the genetic risk

CHAPTER 11

Chromosome 11

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Abstract: Over the years, many scientists and doctors have been treating the deadly cancer disease but cannot find a permanent treatment for this disease. Also, sometimes it becomes tough to understand the mechanisms and causes of cancer as it is a very complex disease that involves many biological processes. Due to the redundancy in our biological system, cancer progression becomes very easy, thus making it difficult to cure. To find the root cause of this disease, we should know what genetic alterations are causing cancer progress and who is participating in these alterations, like proteins, signaling pathways, or genes. Cancer is caused due to various reasons; it can be due to genetics but primarily due to carcinogens, causing mutations in the genes, thereby making them an oncogene. The Proto-oncogenes are those genes that usually assist the growth of tumor cells. The alteration, mutation, or increased copy number of a particular gene may turn into a proto-oncogene, which could end up completely activated or turned on. Many Tumor-causing alterations or mutations related to oncogenes are usually acquired and not inherited. These tumor-causing mutations often actuate oncogenes *via* chromosomal rearrangement or changes in the chromosome, which sequestrates one gene after another, thereby permitting the first gene to prompt the alternative. Search which genes are involved in different cancer types would help scientists proceed with new methods for finding a cure for this disease. This article will depict which genes and their location on which chromosomes, specifically on chromosome 11, are related to different types of cancer.

Keywords: Cancer, Chromosome 11, Chromosome Rearrangements, Gene Duplication, Mutation, Oncogene, Proto-oncogene.

1.1. GENE - NUP98; NUCLEOPORIN 98. LOCATION - 11p15.4.

NPCs alter the shipping of macromolecules among the cytoplasm and nucleus and are made up of several polypeptide subunits, many of which belong to the nucleoporin class or family. NPCs belong to the nucleoporin family that codes for 186-

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kDa precursor-protein that encountersautoproteolytic-cleavage toform a 98kDa and 96kDa nucleoporin. The ninety-eight kDa nucleoporin includes a repetition of the Gly-Leu-Phe-Gly (GLGF) domain and indulges in many cellular mechanisms, such as nuclear export, mitotic progression, nuclear import, and activation of gene expression. The 96kDa nucleoporin is more or less a scaffold factor of NPC. Proteolytic cleavage is critical for targeting the proteins to NPC. Translocations among the NPC gene and many companion genes have been located in several leukemias. Rearrangements commonly bring chimeras with the N-terminal GLGF area of this NPC gene to the C terminus of the companion gene. The alternative-splicing consequences in a couple of transcript mutations or variants encoding several isoforms, as a minimum of 2 that are proteolytically-processed. Some variants here lack the area that encodes for the ninety-six kDa nucleoporin. The mammalian genes have been established to amalgamate several genes following chromosome translocations in T-cell acute-lymphocytic leukemia and acute-myelogenous leukemia. The NUP98 gene is among numerous genes placed within the imprinted-gene area of 11p15.5, an important tumor-suppressor gene area. The alterations in this area are usually correlated with adrenocortical carcinoma, Wilms tumor, ovarian tumor, Beck with-Wiedemann syndrome, breast cancer, rhabdomyosarcoma and lung cancer. The study of AML childhood suf-ferers from Austria diagnosed one NUP98 gene rearrangement in fifty-nine unselected instances. A study intended to identify the NUP98-HOXA9 fusion found that three of two hundred and eight unselected acute-myelogenous cases of leukemia had NUP98-HOXA9 fusion in the Asian group population [1, 2]. Fusion, NUP98-HOXA9 was diagnosed in sufferers with CML-bc (Ph+), and the combined nature of BCR-ABL and NUP98-HOXA9 fusions was established in the experimental mouse model [3, 4].

1.2. GENE - CCND1; CYCLIN D1 LOCATION - 11q13.3

The protein coded through CCND1-gene belongs to the cyclin family, which is notably very conserved. Its contributors are often characterized by elevated protein abundance during the cycle. Cyclins usually function as actuators of CDK kinases. Various cyclins showcase defined patterns of degradation and expressions that contribute to the temporal coordination of every mitotic event. The cyclin D1 configures a complex and actuates as a regulatory or activation subunit of CDK6 or CDK4, whose activation is essential and, indeed, required for the transition phase of the cell cycle (G1/S phase). The protein-CCND1 has been demonstrated to interact with Rb protein, a tumor suppressor. The over-expression, alteration, and mutations of CCND1 involved in the alteration of cell cycle progression are majorly found in several types of cancers, which further contribute to tumorigenesis and oncogenesis. CCND1 actuates as an oncogene

and is frequently over-expressed in many cancers through gene rearrangement or amplification [5 - 7]. The CCND1 alterations inhibiting ubiquitin-mediated degradation, nuclear export, and Thr286 phosphorylation *via* the proteasome have activated the CDK6/4 network, thereby enhancing the malignant transformation and cellular proliferation both *in vivo* and *in vitro* [8 - 10].

1.3. GENE -BIRC3; BACULOVIRAL-IAP REPEAT CONTAINING-3. LOCATION - 11q22.2

BIRC3 gene codes a particular member of the IAP family of proteins that inhibits apoptosis by forming a complex with tumor-necrosis factor receptor-associated elements TRAF2 and TRAF1, possibly *via* interfering with the actuation of ICE-like proteases. The encoded protein hinders apoptosis through the means of serum deprivation; however now no longer affects apoptosis as a consequence of exposure to menadione, a vigorous inducer of free radicals. It incorporates three baculovirus repeats of IAP and a ring-finger domain. Transcript-variants coding the identical isoform had been identified. BIRC3 can potentially enhance the therapeutic resistance in Glioblastoma [11]. GBM survival is enhanced by the functional contribution of BIRC3 *via* its mechanism in hindering the actuation of caspases [12, 13]. Still, it promotes inflammatory techniques *via* the mediation of tumor-necrosis-factor α signaling [14 - 18].

1.4. GENE - POU2AF1; POU-CLASS 2 HOMEOBOX-ASSOCIATING FACTOR 1 LOCATION - 11q23.1

The protein is likewise termed as an Oct co-activator from B cells, aka Oct binding complex, and as generally discovered withinside the literature, BOB1. BOB1 is a transcriptional co-activator expressed basically *via* B-cell lymphocytes and mastery of immunoglobulin and different genes essential for those cell's expressions of CRISP-3, CD20, and CD36 [19]. The regulation of BOB1 has been verified beneficial for figuring out positive lymphomas, such as B-cell lymphomas, as typified in research that uses BAB1 expression to assist perceive lymphomas [19]. The increase in copy number of POU2AF1 was identified in 3 out of 23 patients, informing that the POU2AF1 amplification is not the artifact obtained at the time of establishing a cell line. However, an infrequent POU2AF1 amplification was detected in a small range of cases. However, the frequent amplification of the POU2AF1 gene in MM isn't so low as compared with different gene amplification activities: for instance, the MYCN amplification, one of the essential genetic activities figuring out analysis in neuroblastoma, is thought to be located in much less than 20% on this disease [20].

CHAPTER 12

Chromosome 12

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Abstract: Chromosome 12 spans about 134 million DNA building blocks and represents approximately 4.5 percent of the total cellular DNA. Gene dysregulation from chromosome 12 has triggered a cell to transform into a cancerous cell. Different types of genes are present in chromosome 12 that cause colon cancer, ovarian cancer, prostate cancer, ampulla of Vater cancer (Vater cancer), *etc*. These genes play their role in the development and the progression of cancer into metastasis, Epithelial to mesenchymal transition, and overall cancer growth. In this chapter, we have enlisted the genes responsible for cancer and their short introduction.

Keywords: Cancer, Cancerous Cell, Colon Cancer, Cancer Growth, Downregulated, Epithelial-Mesenchymal, Gene Dysregulation, Metastasis, Ovarian Cancer, Prostate Cancer.

1.1. A2M – ALPHA-2-MACROGLOBULIN, CHROMOSOME 12; 12p13.31

The protein encoded by this gene is a protease inhibitor and cytokine transporter. It uses a bait-and-trap mechanism to inhibit a broad spectrum of proteases, including trypsin, thrombin and collagenase. Downregulated DEGs of *A2M* were significantly associated with the "Complement and coagulation cascades" pathway and the "Ras signaling pathway." Downregulated A2M might contribute to the progression of Bladder Cancer [1]. *A2M* out of the seven predicted gene markers was found to encode proteins secreted into urine, providing potential diagnostic evidence for pancreatic cancer [2].

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1.2. A2LM1 - ALPHA 2 MICROGLOBULIN LIKE 1 CHROMOSOME 12; 12p13.31

A2ML1, which are under-expressed in the ER+ group and over-expressed in the ER− group. *A2ML1* which encodes the secreted protease inhibitor α-2-M [A2M]-, like-1 activates mutations in signal transducers of the RAS/mitogen-activated protein kinase [MAPK] pathway [3].

1.3. AACS-ACETOACETYL-COA SYNTHETASE CHROMOSOME 12; 12q24.31

Acetoacetyl-CoA synthetase [AACS] is the enzyme responsible for cholesterol and fatty acid synthesis in the cytosol. *AACS* dysregulation by Sp1 has been reported in neuroblastoma cell lines. AACS gene has been reported in Vater cancer. A small opening connecting the pancreas and bile ducts to the duodenum is called the ampulla of Vater. Mutation in the *AACS* gene (Fig. **1**) causes cancer in this Ampulla of Vater. AACS protein is related to Valine, isoleucine, and leucine degradation pathways. AACS protein is also linked to Ketone body metabolism [4].

1.4. ABCB9 - ATP-BINDING CASSETTE, SUBFAMILY B, MEMBER 9 CHROMOSOME 12; 12q24.31

Paclitaxel is widely used in treating breast cancer; drug resistance increases the failure of chemotherapy. Using microRNA target prediction tools, they have identified that *ABCB9* could be one of the target genes of miR-24. miR-24 can also affect the expression of *ABCB9* to regulate the sensitivity toward paclitaxel of breast cancer cells. It was identified that miR-24 could directly bind to the 3′-UTR of ABCB9, thereby inhibiting the translation of *ABCB9* [5].

1.5. ABCC9 - ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9 CHROMOSOME 12; 12p12.1

ABC transporters play a major role in prostate cancer [PCa] development, and the *ABC* transporter gene expression was analyzed in PCa and noncancerous prostate tissues [NPT]. ABCA8, ABCB1, ABCC6, ABCC9, ABCC10, ABCD2, ABCG2, and ABCG4 expression of eight ABC transporter genes were down-regulated in the absence of the TMPRSS2- ERG fusion transcript Prostate cancer [PCa] as compared to Noncancerous prostate tissue [NPT], and only two genes [*ABCC4* and *ABCG1*] were up-regulated [6].

1.6. ABCD2 - ATP-BINDING CASSETTE, SUBFAMILY 3, MEMBER 2 CHROMOSOME 12; 12q12

X-linked adrenoleukodystrophy [X-ALD] is a peroxisomal disorder which is caused by mutations in the *ABCD1* gene that encodes the peroxisomal ATP-binding cassette [ABC] transporter subfamily D member 1 protein [ABCD1], which is also referred to as the adrenoleukodystrophy protein [ALDP]. Induction of the *ABCD2* gene, which is closest to ABCD*1*, has a possible therapeutic option for the defective ABCD1 protein in X-ALD. X-ALD is caused by mutations that occurred in the *ABCD1* gene, which is also associated with the accumulation of VLCFAs [Very Long Chain Fatty Acids] in the plasma and tissues of the patients, Induction of *ABCD2* can be a better treatment option for X-ALD because expression of this protein can decrease VLCFAs [Very Long Chain Fatty Acids] levels in fibroblasts [7].

1.7. ACRBP - ACROSIN-BINDING PROTEIN CHROMOSOME 12; 12P13-p 12

Myxoid and round cell liposarcoma are formed in soft and fat tissues. Cancertestis antigens are immunogenic antigens that have an expression restricted to testicular germ cells and malignancies, making them attractive targets for cancer immunotherapy. Gene expression studies reported that expression of various cancer-testis antigens in liposarcoma, with mRNA expression of CTAG1B, CTAG2, MAGEA9, and PRAME, are described in myxoid and round-cell liposarcoma. Overexpression of *NY-ESO-1* in myxoid and round cell liposarcoma, the expression of cancer-testis antigens evaluated are MAGEA1, ACRBP, PRAME, SSX2, and by immunohistochemistry and PRAME, CTAG2, and MAGEA3 by quantitative real-time PCR [8].

1.8. ACSS3 - ACYL-COA SYNTHETASE SHORT CHAIN FAMILY, MEMBER 3CHROMOSOME 12; 12q21.31

Gastric cancer [GCa] is one of leading cancer in humans. Mitochondrial-derived acetyl-CoA contributing enzymes [acyl-coA synthetase super-family 3; ACSS3] are patient's progression of Gastric Cancer [GCa]. Cholesterol is an essential component for fast-growing cancer cells. The mevalonate pathway is an enzymatic cascade that is responsible for de novo cholesterogenesis. *ACSS3* is a landmark cancer progression gene in Gastric Cancer [GCa] patients, which is part of the biochemical process for the mitochondrial production of acetyl-CoA [9].

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