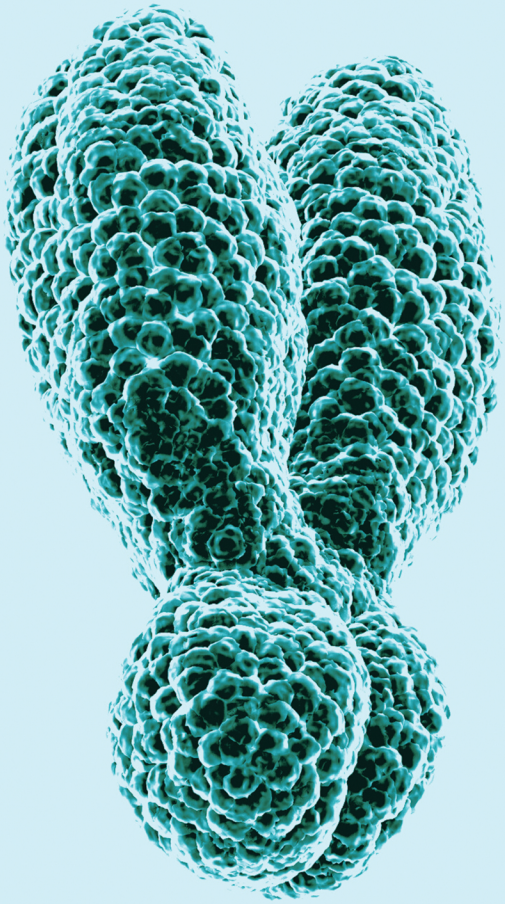
A COMPILATION OF GENES IN EACH CHROMOSOME

CANCER GENES



SATISH RAMALINGAM
EDITOR

Bentham Books

Cancer Genes

(Volume 2)

Edited by

Satish Ramalingam
Department of Genetic Engineering, School of Bioengineering
SRM Institute of Science and Technology
Kattankulathur-603203
India

Cancer Genes (Volume 2)

Editor: Satish Ramalingam

ISBN (Online): 978-981-5136-50-0

ISBN (Print): 978-981-5136-51-7

ISBN (Paperback): 978-981-5136-52-4

First published in 2023.

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
80 Robinson Road #02-00
Singapore 068898
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

PREFACE

Cancer is a disease that affects millions of people worldwide, and the research for its cure has been ongoing for decades. In recent years significant progress has been made in identifying specific genes that are associated with an increased risk of developing cancer. In the continuation of our exploration of cancer-causing genes, we present volume 2 of our book. This volume picks up where volume 1 left off and delves into the genetic mutations that are located on chromosomes 13-22, as well as the X and Y chromosomes. We delve into the latest research on these genes, and the ways in which they contribute to cancer development. This volume provides a comprehensive overview of the cancer-causing genes located on chromosomes 13-22, as well as the X and Y, and serves as an invaluable resource for researchers, medical professionals, and anyone interested in the genetic basis of cancer. Together, both volumes provide a complete and in-depth understanding of the cancer-causing and their location on each chromosome.

Satish Ramalingam
Department of Genetic Engineering, School of Bioengineering
SRM Institute of Science and Technology
Kattankulathur-603203
India

List of Contributors

Abhishek Mitra	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Advait Sohan	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Aishwarya Raja	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Anusha Mandem	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Chandrakumar Subramanian	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Harini Hariharan	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Jayasree Debnath	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Kakaraparthi Shradda	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Ravi Gor	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Satish Ramalingam	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Saurav Panicker	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Sayooj Madhusoodanan	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Sivasankari Ramadurai	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Sowmiya Sattanathan	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203
Thilaga Thirugnanam	Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India 603203

CHAPTER 1

Chromosome 13

Aishwarya Raja[1], Ravi Gor[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: Chromosome 13 represents around 4 percent of the total cellular DNA with 115 million base pairs. It is home to various tumor suppressors and oncogenes, such as ADP ribosylation factors like GTPase-11 (ARL11), Retinoblastoma-1 (RB1), Ras-related protein Rap-2a (RAP2A), *etc*. Most of the somatic mutations in this chromosome lead to cancer development. Further, deletion in this chromosome has been reported to support the cancer of leukemias, lymphomas, *etc*. In this chapter, we have tried to list cancer-causing genes and their possible oncogenesis in cancer development.

Keywords: ADP Ribosylation Factors Like GTPase-11, Cancer, Gene Deletion, Leukemia, Lymphomas, Oncogene, Ras-Related Protein Rap-2a, Retinoblastoma-1, Tumor Suppressor, Tumor Suppressor.

1. ABCC4- ATP BINDING CASSETTE SUBFAMILY C MEMBER 4 CHROMOSOME 13; 13q32.1

ATP-binding cassette sub-family C member 4 [ABCC4], also known as the multidrug resistance-associated protein 4 [MRP4] or multi-specific organic anion transporter B [MOAT-B], is a protein that in humans is encoded by the ABCC4 gene [1]. MRP4 confers resistance to acyclic nucleoside monophosphates, such as 9-[2-phosphonylmethoxyethyl] guanine [PMEG], and to the anti-HIV drug, 9-[2-phosphonylmethoxyethyl] adenine [PMEA] [2]. ABCC4 protein is present in humans' kidneys, liver, erythrocytes, adrenal glands, platelets, brain, and pancreas [3].

2. ARL11- ADP RIBOSYLATION FACTOR LIKE GTPASE 11 CHROMOSOME: 13; 13q14.2

ARL11, also known as ADP-ribosylation factor-like tumor suppressor gene 1 [ARLTS1], is a member of the Arf-like [ARL] family of small GTP-binding prot-

* **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

eins that regulate diverse cellular processes, including vesicular trafficking, cytoskeletal organization, signaling, and ciliogenesis [4]. Further support for its tumor suppressor function has come from the finding that SNPs G446A [W149X] and T442C [C148R] in the ARL11 gene are associated with familial risk for chronic lymphocytic leukemia [CLL] and breast, prostate, and colorectal cancers [5].

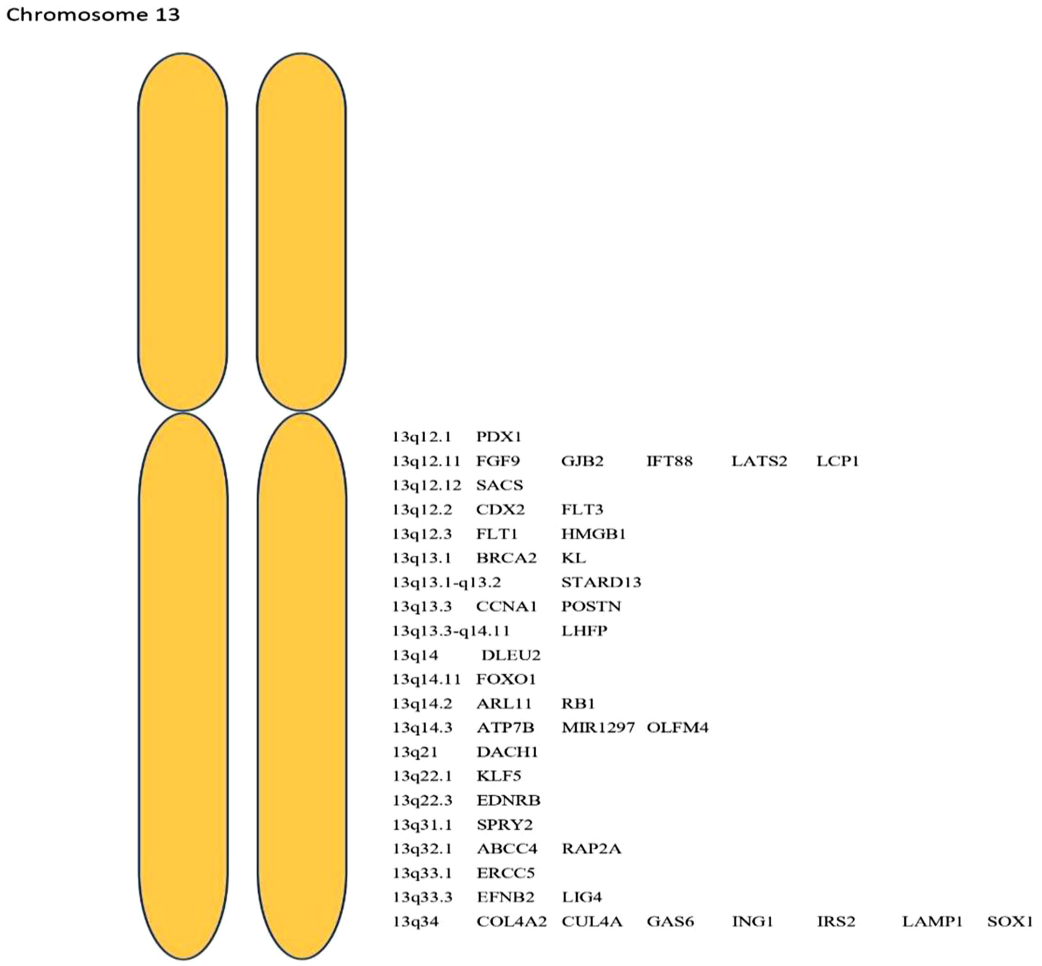


Fig. (1). This figure displays the loci of the genes from Chromosome 13 whose roles in cancer have been explained in this chapter. Sayooj Madhusoodanan designed this diagram.

3. AT7B - ATPASE COPPER TRANSPORTING BETA CHROMOSOME: 13; 13q14.3

This gene (Fig. **1**) is a P-type cation transport ATPase family member and encodes a protein with several membrane-spanning domains, an ATPase consensus sequence, a hinge domain, a phosphorylation site, and at least 2 putative copper-binding sites. This protein functions as a monomer, exporting copper out of the cells, such as the efflux of hepatic copper into the bile. The ATP7B product, a protein of 1465 amino acids [ATP7B], is expressed predominantly in humans' liver, kidney, and placenta [6]. ATP7B was overexpressed in cisplatin-resistant prostate carcinoma PC-5 cells but not in the parental PC-3 cells and the revertant PC-5R cells. ATP7B may be involved in cisplatin resistance in some tumors [7].

4. BRCA2- BREAST CANCER GENE 2 CHROMOSOME 13; 13q13.1

This gene (Fig. **1**) helps make a breast tumor suppressor protein. BRCA2 is involved in repairing damaged DNA by interacting with several other proteins in the nucleus to mend the damaged DNA. Mutations in this gene cause breast cancer [8]. The BRCA2 gene interacts with the recombinase enzyme and stimulates and maintains strand invasion [9]. It is expressed in breast tissues and other cells and destroys cells if the DNA is not repaired [10].

5. CCNA1- CYCLINE A1 CHROMOSOME 13; 13q13.3

The Cycline A1 protein encoded by this gene (Fig. **1**) is expressed in the testis, brain, and several leukemic cell lines and controls meiosis. This protein binds to Rb family proteins, the E2F1 transcription factor and the Kip/Cip family of CDK-inhibitor proteins [11]. They activate the subunits of enzymatic complexes with CDKs [12]. CCNA1 gene-associated diseases include myeloid leukemia and testicular cancer [13].

6. CDX2- CAUDAL TYPE HOMEOBOX 2 CHROMOSOME 13;13q12.2

This gene (Fig. **1**) produces homeobox caudal transcriptional factor protein expressed in the intestinal epithelial cells [14]. It helps in embryonic development, regulation, proliferation and differentiation of intestinal epithelial cells in the adult. CDX2 ectopic expression was found in acute myeloid leukemia [15]. CDX2 is used as a biological marker for detecting intestinal cancer [16]. It is found to be expressed only in intestinal cells.

CHAPTER 2

Chromosome 14

Harini Hariharan[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: Cancer genetics has focused on several mutational events within a tumor cell for many years. Recently, the study on cancer genetics has been widened by concentrating on the importance of intercellular communication and epigenetic events causing tumor progression and development. The translocation of genetic material betwixt chromosome 14 and other chromosomes may engender the formation of various types of tumors. Recent studies emphasize that these chief translocations between two chromosomes may disrupt the genes crucial for controlling cell growth and cell division. The translocations involving chromosome-14 and other chromosomes have been found in tumors including acute myeloid Leukemia, acute lymphoblastic leukemia, acute bilineal leukemia, follicular lymphoma, small cell lung cancer, non-Hodgkin's lymphoma, Burkitt lymphoma and multiple myeloma. The tumor suppressor genes, such as ARID4A, ARID4B, BCL11B, BMP4, CCNB1IP1, CEBPE, DICER1, DLK1, ESR2, FOXN3, HIF1A, MAX, MEG3, NDRG2 and TTF-1/NKX2-1 under chromosome 14, play a hypercritical role by enhancing cellular differentiation, migration, proliferation, metastasis, invasion, cellular growth, and development in several tumors, including breast cancer, pancreatic tumor, osteosarcoma, lung cancer, endocrine tumor, T-ALL, cystic nephroma, Hodgkin lymphoma, pleuropulmonary blastomas, Sertoli Leydig ovarian tumors and rhabdomyosarcoma. Chapter 14 meticulously discusses the importance of each predominant gene under chromosome 14 in mediating tumorigenesis. In cancer genetics, these cardinal genes play a crucial role by acting as an oncogene or a tumor suppressor in several cancers. Thus, targeting these tumor-causing genes would provide a breakthrough in cancer biology and oncology when concerned with future perspectives.

Keywords: Burkitt lymphoma, Cellular differentiation, Cystic nephroma, Epigenetic events, Follicular lymphoma, Hodgkin's lymphoma, Intercellular communication, Oncogene, Rhabdomyosarcoma, Translocations, Tumor suppressor.

[*] **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

1. AKT1: AKT SERINE/THREONINE KINASE 1. CHROMOSOME 14; 14q32.33

The three major isoforms of the serine-threonine kinase superfamily include AKT1, AKT2, and AKT3 [1]. AKT1 encodes a protein called PKBα [kinase B alpha protein] [1]. Recent studies emphasize that overexpression of the AKT signaling pathway is observed in almost 50% of human cancers [1].

Abnormal or altered gene expression levels of AKT signaling are predominantly found in tumors such as breast, non-small cell lung cancer, esophageal cancer, leukemic cancer, ovarian, colorectal cancer, and head and neck cancer [1, 2]. The SNPs identified in the AKT1 gene, including E319G rs12881616, P388T rs11555431, L357P rs11555432, E17K rs121434592, rs3803304 and rs2494732, are widely associated with tumor formation and migration [1]. On considering the enginery, the role of the AKT1 gene and its activation in tumor metabolism, recent studies hypothesize that the mTORC2 signaling pathway plays a pivotal role in phosphorylating and activating AKT1 gene at S473 in its carboxy terminus, wherein PDK1 phosphorylates AKT1 gene at T308 in its activation loop [1]. The activated AKT1 gene further phosphorylates certain downstream elements, which regulate tumor metabolism, apoptosis, cell growth, proliferation, and angiogenesis [1, 2]. Among the AKT1-associated SNPs, the rs3803304, an intronic noncoding variant, is superlatively correlated with breast tumor formation and development, suggesting that rs3803304 could be a prognostic biomarker in breast cancer formation [1]. Moreover, the mutation of $AKT1^{E17K}$ is found to be associated with HR-negative cancer cells with the relapsed condition [2]. Interestingly, the mutation of $AKT1^{E17K}$ is not interrelated with lobular, medullary, ductal and mucinous histotypes [2]. The activation of the AKT gene in breast tumor cells showed elevated resistance to tamoxifen and trastuzumab treatment [3]. Higher expression of AKT is associated with early stages of sporadic colorectal carcinogenesis [4]. AKT1 gene expression is also mediated by Wnt/β-catenin signaling pathways [4]. The AKT1 transcription is mainly mediated by Tcf-Lef/ β-catenin in colorectal cancer [4]. Thus, the elevated expression of the AKT1 gene is associated with increased levels of nuclear β-catenin in sporadic colorectal cancer [4]. The amplification of AKT1 was first found in gastric cells, wherein in lung tumor cells, the AKT1 amplification leads to cisplatin resistance *via* the activation of the mTOR signaling pathway [3]. Though the regulation and activation of the AKT gene are almost found in 90% of non-small cell lung carcinoma, the $AKT1^{E17K}$ mutation transformation happens at a very low level in NSCLC [3].

2. APEX1: APURINIC/APYRIMIDINIC ENDODEOXYRIBONUCLEASE 1 CHROMOSOME 14; 14q11.2

Redox factor 1, or APEX1, is a protein that possesses multifunctional characteristics and is involved in repairing apyrimidinic sites and ssDNA breaks [5]. APEX1 gene enhances the activation of the DNA-binding machinery of certain transcriptional factors involved in tumor progression and promotion, such as NF-kB, EGR1, PAX8, AP1, HLF, P53, and MYB [5]. Abnormal expression levels of APEX1 are usually associated with various solid tumors and their progression [5]. However, the actuation of the APEX1 gene in cancer progression is a hitherto [5]. Studies postulate that the expression levels of APEX1 are highly correlated with poor prognosis of cervical cancer, prostate cancer, colorectal cancer, osteosarcoma, hepatic cancer, and breast cancer [5]. APEX1 sustains tumor proliferation and cell viability in breast and colon tumor cells [5]. In an ovarian tumor, the depletion of the APEX1 gene attenuates the proliferation activity of the cells [5]. Interestingly, APEX1 implicates an antitumor activity in pancreatic tumor cells, like quelling tumor invasion, migration, and tumor growth [5]. As an upstream regulator and activator of the notch/ jagged1 signaling pathway, the APEX1 gene enhances the behavior of the colon tumor [5]. Meanwhile, elevated levels or knockout of APEX1 expression in colon tumors result in intense alteration of malignant characteristics in tumor cells, such as migration, metastasis, angiogenesis, proliferation, invasion, anchorage-independent growth, and tumor formation [5]. The carcinogenic activity of APEX1 is unraveled by its mode of enginery in up-regulating the jadded1 ligand in the notch signaling pathway [5]. Hence, APEX1 is a potential regulator of the jagged1 ligand and a curative target to treat colon tumors [5]. The mRNA expression levels of the APEX1 gene were notably higher in head and neck cancer cells in juxtaposed with control cells [6]. Surprisingly, the mutation and down-regulation of APEX1 caused a tremendous risk of head and neck cancer [6]. Widely known for its enhancement of DNA-binding machinery, APEX1 triggers the DNA-binding mechanism of NF-kB both *in vitro* and *in vivo* [6]. Depriving the APEX1 redox domain directly quells the TNF- mediated NF-kB regulation, which triggers TNF-mediated apoptosis of cells [6]. Recent studies emphasize that APEX1 expression in tumor cells may begin a perineural invasion and that APEX1 expression is relatively associated with gallbladder carcinoma [CaGB] formation [7].

3. ARID4A: AT-RICH INTERACTION DOMAIN 4A CHROMOSOME 14; 14q23.1

The natural phenomena of the ARID group are to activate transcription and are majorly indulged in cell proliferation and differentiation [8]. Hence, being an essential transcriptional regulator, ARID plays a crucial role in cellular

CHAPTER 3

Chromosome 15

Harini Hariharan[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: The genomic alteration at chromosome 15 has been widely recognized as the utmost significant and prevalent alteration in several cancers, including non-small-cell lung cancer, breast cancer, ovarian cancer, prostate cancer, gastrointestinal cancer, acute lymphoblastic leukemia, colorectal carcinoma, hepatocellular carcinoma, myeloma, pituitary adenomas, *etc*. Emerging reports suggest that the abnormalities of prime genes in chromosome 15 have drastic effects on tumor development and progression, and can be candidate biomarkers of disease prognosis, disease progression, and response to treatment. The translocations involving chromosome 15 and other chromosomes have been found in tumors, including mucoepidermoid carcinomas, mixed-lineage leukemia, colorectal cancer, pancreatic cancer, sarcoma, lung adenocarcinoma, melanoma, brain cancer, cholangiocarcinoma, spitz tumor, congenital mesoblastic nephroma, papillary thyroid cancer, pontine glioma tumors, and acute promyelocytic leukemia. The tumor suppressor genes such as C15orf65, CSK, CRABP1, DAPK2, FES, GREM1, KNSTRN, NEDD4-1, NTRK3, PML, SPRED1, TPM1, and TCF12 under chromosome 15 play a crucial role by enhancing cellular growth, proliferation, migration, invasion, metastasis, cellular differentiation, and development in various cancer, including colorectal cancer, acute promyelocytic leukemia, myeloid leukemia, breast cancer, thyroid carcinoma, glioblastoma, intrahepatic cholangiocarcinoma, chondrosarcoma, cartilaginous cancer, Squamous cell carcinoma, non- small-cell lung carcinomas, mucosal melanoma, and oral squamous cell carcinoma. Chapter 15 discusses the significance of each important gene under chromosome 15 in mediating oncogenesis. The elevated or attenuated expression levels of these cardinal genes can either act as an oncogene or a tumor suppressor. Thus, shedding light on these genes would be a game changer in the field of cancer genetics and theragnostic.

Keywords: Biomarkers, Cholangiocarcinoma, Hepatocellular carcinoma, Lymphoblastic leukemia, Mesoblastic nephroma, Mixed-lineage leukemia, Molecular-abnormalities, Mucoepidermoid carcinomas, Oncogenesis, Pontine glioma, Prognosis, Promyelocytic leukemia, Spitz tumor, Thyroid cancer, Tumor-development.

[*] **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

1. ADAM10: A DISINTEGRIN AND METALLOPROTEINASE DOMAIN-CONTAINING PROTEIN 10 CHROMOSOME 15; 15q21.3-q22

ADAM10 is a dis-integrin-metalloproteinase known for its role in shedding the extracellular domain of transmembrane proteins [1]. ADAM10 is an Alzheimer's disease susceptible gene. ADAM10 has been implicated in the shedding of substrates, including Notch receptor, HER2, E-cadherin, CD44, L1-CAM, EGFR ligands, EGF, ErbB2/ERK, betacellulin, and inflammatory cytokines [1]. Non-amyloidogenic α-secretase activity plays a key role in ADAM10- mediated proteolysis [1]. These substrates cleaved by ADAM10 result in cancer initiation, progression, and migration, above which the Notch signaling pathway plays a major role in the initiation and progression of lung cancer [1]. GI254023X, a selective inhibitor of ADAM10, is found to reduce the migration and invasion of breast cancer cells [2].

2. ANXA2: ANNEXIN A2 CHROMOSOME 15; 15q22.2

Intracellular ANXA2 plays a vital role in endocytosis, exocytosis, and membrane trafficking, wherein the knockdown of ANXA2 inhibits cell division and proliferation [3]. Extracellular ANXA2 helps in phagocytosis, fibrinolysis and anticoagulation, angiogenesis, and cell metastasis [3]. ANXA2 interacts with plasminogen and tPA, resulting in plasminogen-to-plasmin conversion mediating the lysis of fibrin polymers [3]. As a result, the degradation of the extracellular matrix promotes cell invasion and migration [3]. Abnormal ubiquitination of ANXA2 leads to overexpression of the gene-inducing metastasis of breast cancer [3]. By blocking the ANXA2 surface with a specific antibody, tumor cell growth can be inhibited [3]. ANXA2 is overexpressed in acute lymphoblastic leukemia [ALL], APL, breast cancer, and colorectal carcinoma [CRC] [4].

3. ANP32A: ACIDIC LEUCINE-RICH NUCLEAR PHOSPHOPROTEIN 32 FAMILY MEMBER A CHROMOSOME 15; 15q23

Acidic leucine-rich nuclear phosphoproteins are the important regulators of tumorigenesis. ANP32A potentially interacts with SET, KLF5, pRB, NM23H1, and Axin-1 [5]. ANP32A is recognized as a positive prognostic marker in non-small-cell lung cancer, where reducing its expression increased ras-induced tumorigenicity of NIH3T3 cells [5]. ANP32A expressions are highly increased in colorectal, ovarian, and prostate cancers. However, ANP32A served as a negative prognostic marker in hepatocellular carcinoma and myeloma [5]. The ANP32A proteins are hypothesized as a double-edged sword in cancer progression due to their role in activating caspase-mediated cell death [5]. ANP32A [HPPCn] was

the first factor that acted as an autocrine factor to promote DNA synthesis and suppress apoptosis by upregulating myeloid cell leukemia 1; this mechanism acts as a hallmark for the cells to proliferate and invade [6].

4. AKAP13: A-KINASE ANCHOR PROTEIN 13 CHROMOSOME 15; 15q25.3.

AKAP13 encodes a member of the AKAP family that coordinates and binds with protein kinase A [PKA] [7]. AKAP13 is a guanine nucleotide exchange factor [GEF] that binds with cAMP-dependent protein kinase and catalysis Rho GTPase activity [7]. This gene encodes the lymphocyte blast crisis oncogene and is hence termed AKAP- Lbc [7]. BRX [breast cancer nuclear receptor binding auxiliary protein], a proto-oncogene encoded by AKAP13, causes breast cancer, and proto lymphoid blast crisis oncogene [proto-Lbc] truncated from BRX causes acute-phase chronic myeloid leukemia [7]. RhoA GTPase is overexpressed in breast cancer cells that trigger different intercellular pathways leading to activation of serum response factor, nuclear factor NF-kB, JNK1, and p38 transcriptional factors [7]. Among the putative influence of Arg494Trp, Asn1086Asp, and Gly2461Ser and the novel influence of Lys526Gln polymorphic non-conservative amino acid in AKAP13, the effect of Lys526Gln variant in AKAP13 shows an increased risk of breast cancer [7]. Tissue transglutaminase [tTG] is considered a high-level phenotypic biomarker that is downregulated in prostate cancer [8]. The interactions between AKAP13 and tTG trigger prostate cancer, and little is known whether AKAP13 is involved in NMDA [N-methyl-D-aspartate] receptor-mediated effect on tTG expression [8].

5. BUB1B: BUB1 MITOTIC CHECKPOINT SERINE/THREONINE KINASE BETA CHROMOSOME 15; 15q15.1.

BUB1B is a protein localized to the kinetochore and inhibits anaphase-promoting complex/cyclosome [APC/C] [9]. An increased expression of the BUB1B gene indicates a high risk of ductal breast carcinoma [10]. Human BUB1B [hBUB1B] is also found to carry mutations in colon cancer [9]. Negative mutation in hBUB1 can reverse the growth arrest in Brca2 deficient cells, eventually leading to neoplastic transformation [9]. BUB1B mutations are reported to have a high risk of embryonal tumors and chromosomal mis-segregations as well [11]. Biallelic mutations in the sacsin molecular chaperone [SACs] gene BUB1B causes MVA [Mosaic variegated aneuploidy] and childhood tumors [11]. BUBR1, the protein encoded by BUB1B is a part of the anaphase inhibitory complex MCC that includes MAD2. MAD2 is the main target of TRIP13's remodeling activity in mitosis [11]. Thus, the mutation in TRIP13 develops Wilms tumor in childhood [11].

CHAPTER 4

Chromosome 16

Sivasankari Ramadurai[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: Cancer is a heterogeneous disorder with invasive and metastatic potential. It is a deadly disorder affecting 1 in 6 people worldwide. Hence, it is important to eliminate the disease. Genetic alterations remain an underlying cause of cancer, and several gene mutations were involved in causing different types of cancer. Recently, researchers have been investigating the role of genetic mutations in causing cancer. For this reason, the genes associated with chromosome 16 were investigated for their role in causing cancer. This study revealed 70 genes associated with cancer. Of which, the cadherin genes (*CDH11*, *CDH13*, *and CDH1*), *AXIN-1*, *ANKRD11*, *BANP*, *CYLD*, *CBFA2T3*, *IR8*, *MVP*, *MT1F*, *NQO1* and *PYCARD* was the tumor suppressor, and the gene *MSLN* is the potential oncogene. *CBFB* and *MYH11* are well-known fusion genes associated with this chromosome. Loss of heterogeneity was noted in the q arm of this chromosome. The chromosome translocations, t (16;16) (16) (p13q22), t (16;21) (21) (p11;q22), t (12;16) (q13; p13; p11), t(16;21) (p11;q22) and t(7;16) (q33; p11) led to the development of acute myeloid leukemia, leukemia, and sarcoma. Several other genes associated with chromosome 16 responsible for cancer initiation and proliferation are summarized in this chapter. A novel insight into the genetic biomarkers and therapeutic targets has been provided to develop potential therapeutic strategies against cancer.

Keywords: ABC superfamily, Biomarker, Cancer, Chromosome 16, Genes, Loss of Heterogeneity, Oncogene, Proto-Oncogene, Therapeutic Target, Translocation, Tumor, Tumor Suppressor.

1. ABCC1: ATP BINDING CASSETTE SUBFAMILY C MEMBER 1 CHROMOSOME 16; 16p13.11

This gene encodes a protein that is a member of the ATP binding Cassette (ABC) superfamily transporters. This transporter is a member of Multi drug resistance protein (MRP) subfamily [1]. *ABCC1* is expressed ubiquitously in all the tissues and protects the tissues by maintaining normal physiology [2]. *ABCC1* overexpression in cancer tissues has been reported to be associated with drug resistance in

* **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

leukemia, lung cancer, esophageal cancer, and neuroblastoma developing in childhood [1]. Increased *ABCC1* expression was also found to be associated with the loss of the *p53* function [3]. It was found that Notch1 regulates the expression of this gene. Inhibiting Notch-1 was found to down-regulate the expression of the *ABCC1* gene in cultured MCF7/VP cell lines [4], and it was stated that the *ABCC1* promoter was hypo methylated in pancreatic cancer cells. It was correlated with tumorigenesis in pancreatic cancer cells and drug resistance, especially in the pancreatic cancer cells that were resistant to the Gemcitabine drug [5]. Also, the overexpression of the efflux pump (MRP-1-ABCC1) plays an important role in contributing to chemoresistance in renal cell carcinoma [6].

2. AXIN 1: AXIS INHIBITION PROTEIN CHROMOSOME 16; 16p13.3

AXIN-1 is the component of the beta-catenin destruction complex, regulating the CTNNB1 Levels and modulating Wnt signaling [7]. It functions as a tumor suppressor and controls cell growth, apoptosis, and development [8]. *AXIN-1* gene deletion or disruption was found to induce hepatocarcinoma [9], and it functions in the Canonical Wnt pathway, and its alterations were associated with some cancers. As the *AXIN-1* gene was found to regulate the expression of CTNNB1, it has been identified that the *CTNNB1* mutations were found to be common among colorectal cancers encoding a defective β-Catenin [7]. A recent study depicted that the complete loss of *AXIN-1* was found to play a role in predisposition to hepatocarcinoma in a mouse model [9]. Different *AXIN* gene polymorphisms were reported in prostate cancer patients having dysregulation in Wnt signaling [10]. When wild-type *AXIN-1* was incorporated *via* adenovirus-mediated gene transfer, it induced apoptosis in Colorectal and hepatocellular cancer cells [11]. Furthermore, *AXIN-1* was one of the mutation targets in Oral squamous cell carcinoma and cytoplasmic accumulation of β-catenin was a characteristic feature in Oral squamous cell carcinomas [12], and reduced expression of this gene was correlated with tumorigenesis in esophageal squamous cell carcinoma [13].

3. AMFR: AUTOCRINE MOTILITY FACTOR RECEPTOR CHROMOSOME 16; 16q13

AMFR is an E3-ubiquitin ligase that degrades protein through proteasomal degradation *via* endoplasmic reticulum-associated degradation (ERAD) [14]. It was involved in promoting the progression of endometrial cancer by targeting the G-protein coupled estrogen receptor 1 (GPER-1) and triggered the phosphoinositide-3-kinase signaling leading to the growth of endometrial cancer [15]. MiR-139-5p acts as a potential tumor suppressor by inhibiting migration and invasion of colorectal cancers by downregulating the expression of AMFR and

NOTCH 1 [46]. When breast cancer tissues were examined for AMF and AMFR transcripts the expression was higher in breast cancer patients who died of breast cancer than in normal tissues. Hence, AMF-*AMFR* overexpression was found to play an important role in breast cancer progression [17]. In gastric cancers, weak E-cadherin and strong AMFR levels expressed a very aggressive phenotype and were found to have a shorter lifespan than those with strong E-cadherin and weak AMFR expression [18]. Thus, it was specified that *AMFR* dysregulation leads to the development of aggressive cancer phenotype. The levels of AMF and AMFR mRNA in liver cancers helped predict the severity of the liver cancer (Fig. **1**).

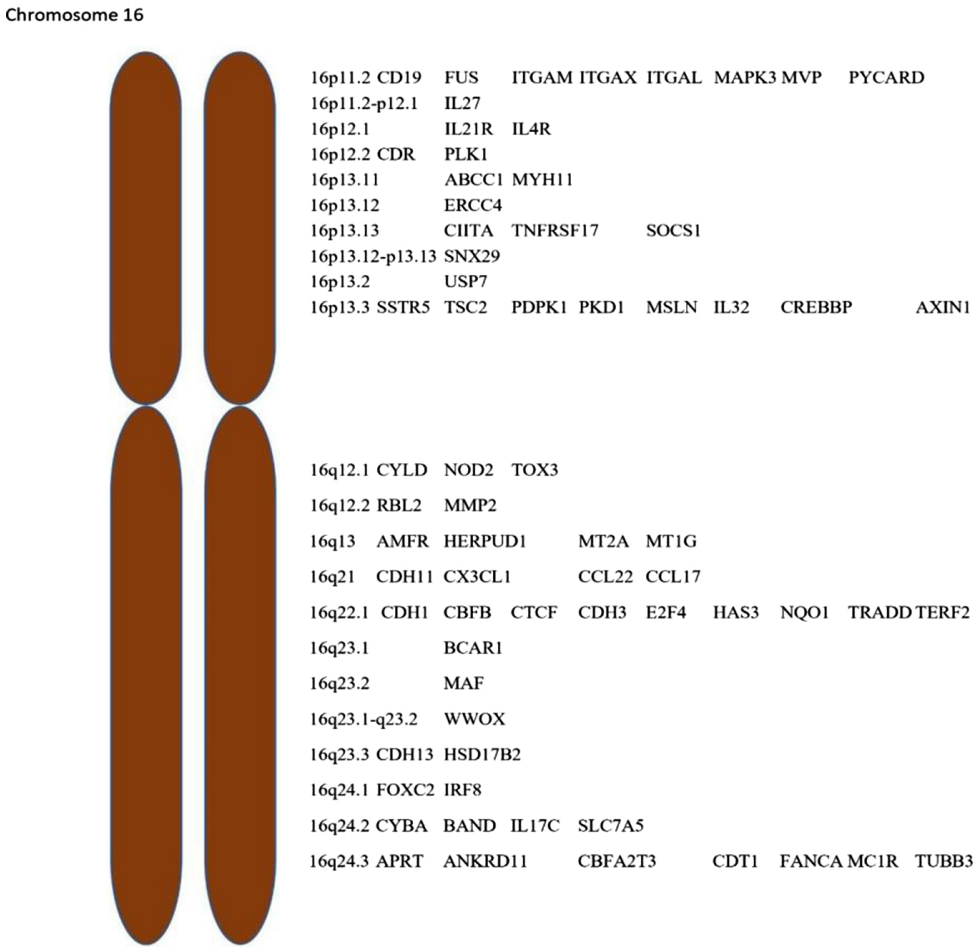


Fig. (1). This figure displays the loci of the genes from Chromosome 16 whose roles in cancer have been explained in this chapter. Sayooj Madhusoodanan designed this diagram.

CHAPTER 5

Chromosome 17

Jayasree Debnath[1,#], Kakaraparthi Shradda[1,#], Thilaga Thirugnanam[1], Advait Sohani[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: Cancer is a disease in which the body's cells divide disorderly and are likely to spread to other organs. It has always been one of the world's top causes of death. A growing population, low mortality rate, and lifestyle changes lead to an increase in the number of cancer cases. It can be caused by genetic or environmental factors or a combination of both. The risk of cancer increases with age as the body loses its ability to eliminate the damaged cells. Cancer-causing genes can be inherited or acquired due to exposure to carcinogens. Cancers are inherited when a mutation occurs in the germ cells. The carcinogens can alter the DNA of a normal gene (a proto-oncogene) converting it into a cancerous oncogene. Genes that slow cell division, fix DNA errors, or undergo programmed cell death (apoptosis) are tumor suppressor genes. Tumor suppressor genes that don't function properly can cause cells to develop out of control, leading to cancer. Cancer expresses itself differently in each individual, making it challenging to identify and treat. Studying the types of genetic mutations, as well as the genes, proteins, and signaling pathways involved in cancer formation will help better understand the underlying cause of cancer. Identifying which genes are expressed in various cancer types will enable scientists to develop novel techniques for curing the disease. This chapter will explain how different cancer types are linked to specific genes and their locations on chromosome 17.

Keywords: Apoptosis, Cancer, Cell Division, Cancer Formation, DNA Damage, Gene, Genetics, Mutations, Oncogene, Signaling Pathway, Tumor Suppressor Gene.

1. ASPSCR1 - ASPSCR1 TETHER FOR SLC2A4, UBX DOMAIN-CO--TAINING CHROMOSOME 17; 17q25.3

The UBX domain of the ASPSCR1 protein interacts with the glucose transporter type 4 [GLUT4]. Without insulin, the ASPSCR1 protein stores GLUT4 in fat and muscle cell intracellular vesicles.

[*] **Corresponding author Satish Ramalingam**: Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

[#] equal authorship and equal contribution status.

However, ASPSCR1 transports GLUT4 to the plasma membrane when insulin is expressed. ASPSCR1 is also known as TUG1. In Osteosarcoma, TUG1 regulated the miR-212-3p/ FOXA1 axis leading to cell proliferation and suppression of apoptosis, suggesting that the axis might be a potential therapeutic target [1]. In renal cell carcinoma and alveolar soft part sarcoma, ASPSCR1 translocates with the TFE3 gene, a transcription factor, at the t[X;17] [p11; q25] locus to yield ASPSCR1-TFE3, a fusion protein with morphological alterations such as psammoma bodies, unique cell wall, bulky cytoplasm, and alveolar growth [2].

2. HLF - HLF TRANSCRIPTION FACTOR, PAR BZIP FAMILY MEMBER CHROMOSOME 17; 17q22

The HLF gene codes for a basic leucine zipper transcription factor that belongs to the proline and acidic-rich [PAR] protein family. To trigger transcription, the HLF protein forms homodimers or heterodimers with other PAR family members and binds sequence-specific promoter regions. B-lineage acute lymphoid leukemia is caused by the chromosomal translocation of the HLF gene with the E2A gene. Cases defined by PAX5 and CRLF2 fusions; point mutations in PAX5 [p.P80R]; point mutations in IKZF1 [p.N159Y]; IGH–CEBPE fusion or mutations in ZEB2 [p.H1038R]; TCF3/4–HLF fusion; and NUTM1 fusions were among the six subgroups in B cell precursor acute lymphoblastic leukemia [BCP ALL], six subgroups included cases characterized by PAX5 and CRLF2 fusions; point mutations in PAX5 [p.P80R]; point mutations in IKZF1 [p.N159Y]; IGH–CEBPE fusion or mutations in ZEB2 [p.H1038R]; TCF3/4–HLF fusion; and NUTM1 fusions [3]. In the hepatoma-derived cell line HLF, a new alternative HAMP transcript was discovered, which was like the wild-type pre-prohepcidin sequence except for the absence of an internal 60-base region [4].

3. COL1A1 - COLLAGEN TYPE I ALPHA 1 CHAIN CHROMOSOME 17; 17q21.33

The COL1A1 gene codes for type I collagen pro-alpha1 chains, which are found in most connective tissues and are particularly abundant in bone, cornea, dermis, and tendon. Mutations in this gene cause Ehlers-Danlos syndrome. Ehlers-Danlos syndrome type VIIA, Caffey Disease, idiopathic osteoporosis, and osteogenesis imperfecta types I-IV are all examples of the classical variety. Reciprocal translocations between chromosomes 17 and 22, where this gene and the gene for platelet-derived growth factor beta are located, are associated with dermatofibrosarcoma protuberans, a kind of skin tumor caused by uncontrolled growth factor expression. For this gene, two transcripts have been found due to the activation of alternate polyadenylation signals. In papillary thyroid cancer [PTC]

progression, the COL1A1 gene co-expressed with hub genes may provide insights into PTC advancement and prospective therapeutic targets for PTC treatment [5]. PPI network analysis identified COL1A1 and nine other hub genes as ten hub genes in gastric cancer [6].

4. ETV4 - ETS VARIANT TRANSCRIPTION FACTOR 4 CHROMOSOME 17; 17q21.31

ETV4 belongs to the member of polyoma enhancer activator 3, a subfamily of Ets transcription factors. ETV4 gene is expressed in diseases such as Ewing Sarcomas and Extraosseous Ewing Sarcomas through LKB1 and RET signaling pathways. While both tumors are cancerous, the former grows in the bones and affects the arms, legs, hips, and spine, whereas the latter attacks the soft tissue in the chest, foot, pelvis, and spine. RNAi and high-throughput screening were used to examine the involvement of ETV5 in PTC proliferation [7]. The three candidate genes [LEF1, ETV4, and FABP6] were co-expressed in tumor samples and substantially linked with colorectal cancer metastasis, according to gene expression analysis using qRT-PCR [8].

5. TAF15 - TATA-BOX BINDING PROTEIN ASSOCIATED FACTOR 15 CHROMOSOME 17; 17q12

TAF15 is a member of the TET family of RNA-binding proteins that play a role in RNA polymerase II gene transcription by building TFIID complexes with transcription initiation factor TFIID. Extraskeletal myxoid chondrosarcoma and acute leukemia are caused by translocations in the TAF15 gene, while mutations cause amyotrophic lateral sclerosis. Ewing Sarcoma, a tiny round cell tumor, is linked to chromosomal translocations between TET/FET [TLS/FUS, EWSR1, and TAF15] and ETS [E26 transformation-specific] family genes [9]. In acute leukemia, the ZNF384 transcription factor is frequently joined to two FET proteins, EWSR1 and TAF15. There is a clear link between the t [12, 17] [p13; q21] rearrangement and the expression of antigen[s], irrespective of the partner gene with which ZNF384 was rearranged [TCF3, EP300, EWSR1, ARID1B, or TAF15] [10].

6. ERBB2 - ERB-B2 RECEPTOR TYROSINE KINASE 2 CHROMOSOME 17; 17q12

ERBB2, a protein belonging to the family of epidermal growth factors (EGF), is a receptor tyrosine kinase involved in downstream signal transduction to upregulate

CHAPTER 6

Chromosome 18

Sivasankari Ramadurai[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: Cancer is an abnormal or unusual growth of cells in the body with invasive and migrating potential. It leads to loss of function, weakens the immune system, and is the second leading cause of death worldwide. This makes it important to eliminate the disease. Genetic predisposition imposes a high relative risk for several kinds of cancer. Inherited genetic mutations are responsible for causing 5 to 10 percent of all cancers. Scientists have investigated mutations in specific genes with more than 50 hereditary cancer syndromes. For this, chromosome 18 was explored for its genes associated with cancer and this study unveiled 30 genes involved in causing cancer. Of these, the genes *DCC, EPB41L3, MBD1 PHLPP1,* and *RBBP8* were the potential tumor suppressors. This chromosome consists of the target genes of the transforming growth factor-beta (TGF-β) signaling pathway. The SMAD family genes *(SMAD4, SMAD7,* and *SMAD2*) are encoded by this chromosome, of which SMAD4 acts as a tumor suppressor. *SERPINB5* and *TCF-4* were the potential oncogenes. The enzyme coded by *TYMS* was a potential therapeutic target for chemotherapy. Several fusion genes of this chromosome (*SS18-SSX2B, SS18-SSX2,* and *SS18-SSX4*) have been identified to cause cancer. Therefore, this chapter provides a summary of the genes in chromosome 18 that are involved in the initiation and proliferation of cancer and provides an insight into the potential biomarkers and therapeutic targets for clinical application to develop a cancer-free world.

Keywords: Biomarker, Cancer, Chromosome 18, Colorectal cancer, Genes, Oncogene, Proto-oncogene, SMAD family, TGF-β signaling, Therapeutic target, Tumor, Tumor suppressor.

1. ADCYAP1: ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE 1 CHROMOSOME 18; 18p11.32

PACAP is the other name for this gene. This gene codes for a proprotein that is secreted and processed further into several mature peptides that trigger adenylate cyclase and elevate cyclic adenosine monophosphate (cAMP) levels, resulting in

* **Corresponding author Satish Ramalingam**: Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

the transcription of target genes. The gene products are significant mediators of stress responses in the neuroendocrine system. Interleukin-6 (IL-6) serum levels were reported to be high in pancreatic ductal adenocarcinoma patients and were considered as an independent risk factor for development and metastasis to the liver [1]. Also, Studies revealed that elevated IL-6 or IL-8 serum level is correlated with hepatic metastasis leading to low survival in these patients [2]. Considering IL-6 as a biomarker for pancreatic cancer, IL-6 was also associated with prostate cancer by activating several pathways of Janus kinases/signal transducers and activators of transcription (*STAT)*, mitogen-activated protein kinases, and phosphatidylinositol 3-kinase aiding in tumor growth and differentiation [3] and the vasoactive intestinal (VIP) and pituitary adenylate cyclase-activating peptides (PACAP) was found to mediate the production of IL-6 in normal prostate epithelial and prostate cancer cells (DU-145/AR prostate cancer and PrEC cells) [4]. Further, the *ADCYAP1* gene is also involved in various biological processes. Its methylation was important for tumor initiation in many cancers, and its promoter's hypermethylation was reported in cervical cancers [5]. Similarly, *ADCYAP1* and *HAND2* gene methylation was found in non-malignant endometrial biopsies that further led to the development of endometrial cancer and served as biomarkers in these patients [6].

2. BCL2: BCL2 APOPTOSIS REGULATOR CHROMOSOME 18; 18q-21.33

This gene (Fig. **1**) is also known as *Bcl-2* and *PPP1R50,* and it encodes an integral outer mitochondrial membrane protein that prevents the apoptotic death of lymphocytes. Translocation of this gene to a heavy chain locus of Ig is expected to cause follicular lymphoma. *P53* and BCL2 proteins were strongly expressed in double-expression Diffuse large B-cell lymphoma (DEL) patients, which can be used for the diagnosis and poor prognosis of DEL [7]. Single nucleotide polymorphism involving rs1016860 of the *BCL2* gene and the genotypes CC, CT, and TT were observed in both breast and gastric cancer. The estrogen and progesterone receptor, Stage, and grade of a tumor with these genotypes were noteworthy in breast cancer and gastric cancer. Especially, the TT genotype was risky in these patients as it led to tumor progression by changing the miR-62--5p's binding to 3'UTR of *BCL2* [8]. *BCL-2* not only serves as a marker for follicular lymphoma but also distinguishes the reactive monocytoid B-cell hyperplasia from marginal zone lymphoma [9]. Elevated Homeobox C6 (*HOXC6*) expression in cervical cancer upregulates *BCL2* leading to antiapoptotic effects that promote the progression of the cell cycle and proliferation of tumor cells [10]. While in Osteosarcoma, *NSD2* was found to regulate the *BCL2* and *SOX2* (apoptosis regulatory proteins) *via* ERK and AKT pathways leading to tumorige-

nesis and chemoresistance in these cells [11]. *CEBPA-AS1*, an oncogene was upregulated in Oral squamous cell carcinoma (OSCC), and this knockdown inhibited the proliferation by CEBPA/BCL2 pathway [12]. Also, HOX transcript antisense RNA (*HOTAIR*) induced the growth of cervical cancer cells by upregulating *BCL2 via* miR-143-3p [13] (Fig. **1**).

3. CDH2: CADHERIN 2 CHROMOSOME 18; 18q12.1

Other names for this gene are *CDHN*, *NCAD*, *CD325*, and *CDw325*. It encodes a traditional cadherin and is a member of the cadherin superfamily. Alternative splicing of this gene results in numerous transcript variants, one of which encodes a pre-proprotein proteolytically processed to a cell adhesion molecule that depends on the calcium and a glycoprotein. This protein aids in establishing left-right asymmetry, nervous system development, and the development of bone and cartilage. Downregulated miR-124 suppressed the *CDH2* gene and was found to promote Epithelial-Mesenchymal Transition in non-small cell lung cancer. This might serve as a potential therapeutic strategy that targets miR-124 and the gene *CDH2* for lung cancer [14]. *CDH2* gene was found to be an activator of epithelial-mesenchymal transition leading to the development of breast cancer. In this case, the expression of miR-708-3p inhibited the expression of this gene, thereby preventing breast cancer metastasis and helping in overcoming chemoresistance [15]. TGF-β-activated the SMAD3/4 complex and were found to trigger the expression of CDH2 by interacting with a SMAD-binding element in the promoter of this gene. This *CDH2* expression induced by TGF-β promoted the epithelial-mesenchymal transition in non-small cell lung cancer. Therapeutic strategies that target SMADs can help overcome from NSCLCs [16]. The polymorphism rs643555C > T alters the expression of CDH2 and influences the biochemical recurrence (BCR) in localized prostate cancer patients after radical prostatectomy (RP). This SNP can be a biomarker to recognize these patients [17]. Further, downregulation of this gene suppressed the metastasis by deactivating the Wnt/β-catenin epithelial-mesenchymal transition (EMT) in hepatocellular carcinoma (HCC) cells [18].

4. DCC: DCC NETRIN 1 RECEPTOR CHROMOSOME 18; 18q21.2

CRC18, *CRCR1*, *MRMV1*, *HGPPS2*, *IGDCC1*, and *NTN1R1* are the other names for this gene (Fig. **1**). It encodes a netrin 1 receptor. This transmembrane protein belongs to the immunoglobulin superfamily of cell adhesion molecules. It facilitates the axon guidance of the growth of neuron cones to sources of the ligand of netrin 1. This protein acts as a tumor suppressor and is repeatedly mutated and downregulated in colorectal cancer and esophageal carcinoma. *DCC*

CHAPTER 7

Chromosome 19

Chandrakumar Subramanian[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: Gene is considered discrete coding units that contain the information for individual proteins. These lot of genes were combined and named DNA which is tightly coiled many times over the histone protein to form Chromosomes. Humans have got 23pairs of chromosomes, including the sex chromosome. The current study is about the major genes and their functions that are present in chromosome 19. There are approximately 1500 genes present in this chromosome, and changes in chromosome 19 are identified in many cancers. Dislocation of the chromosome, a mutation in genes that are present in a chromosome (rearrangements, deletions, or duplications) of DNA in the chromosome, epigenetic modification, and lifestyle changes are some of the chromosomal abnormalities that are responsible for cancer-causing. These changes will trigger the growth of normal cells and induce cancer cell proliferation, migration, invasion, angiogenesis, and metastasis. The signaling pathways like PI3K/AKT, JAK/STAT, NF-κB, and TGF-β are responsible for the various cellular functions with the result of autocrine, juxtacrine, intracrine, paracrine, or endocrine. When the dysregulation of these signaling pathways leads to cancer progression and metastasis. Prostate cancer, breast cancer, gastric cancer, pancreatic cancer, colon cancer, gastric cancer, lung cancer, leukemia, and cervical cancer are the major cancers that are caused because of mutation that occurs in chromosome 19.

Keywords: Histone protein, Mutation, Epigenetic Modification, Proliferation, Migration, Invasion, Angiogenesis, Metastasis, Paracrine, Endocrine, Breast Cancer, Pancreatic Cancer.

1. APOE GENE: [APO LIPOPROTEIN E] CHROMOSOME 19; 19q13.2

ApoE [Apolipoprotein E] is a multifunctional protein, and it plays both major roles in the metabolism of cholesterol and triglycerides and tissue repair and inflammation [1]. ApoE is associated with cholesterol-rich lipoproteins, such as low-density lipoprotein [LDL], and mediates these protein-lipid complexes to bind to the receptors of the LDL receptor. The binding of ApoE and certain LDL receptor family members will initiate signal transduction [2]. ApoE abnormal fun-

* **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

ction is associated with Alzheimer's disease, atherosclerosis and chronic heart disease.

The functions of ApoE have been identified in DNA synthesis, cell proliferation, angiogenesis, and metastasis, so the defect of these functions leads to tumorigenesis and progression. Over-expression of ApoE leads to cancer proliferation and migration in Lung adenocarcinoma and is related to chemore-sistance. ApoE might influence CRC development through three path-ways: cholesterol and bile metabolism, triglyceride and insulin regulation, and prolonged inflammation [3].

2. ALX GENE: [ALX HOMEOBOX] CHROMOSOME 19; 19q13.2

The ALX gene was first found in a patient with chronic myeloid leukemia [CML], and it reveals transformation when overexpressed. The AXL gene has encoded the AXL protein, which is the TAM family of receptor tyrosine kinase receptors. Low expression of AXL in Adults, but the abnormal expression of GAS6/ALX has been found in human malignancies. AXL leads cell proliferation through receptors in the PI3K/AKT/mTOR, RAS/RAF/MEK/ERK, JAK/STAT, and NF-κB signaling pathways. RNAi-mediated knockdown of AXL signaling leads to reduced migration and invasion of cancer cells [4]. AXL made of 894 amino acids with a molecular weight of 140Kda, means equal distribution of amino acids on either side of the plasma membrane. AXL in prostate cancer was highly expressed in metastasis DU145 cells compared with normal prostate cancer cells [5]. AXL is associated with invasiveness and metastasis in lung, Prostate, breast, and gastric cancer and renal cell carcinoma, and Glioblastoma. Overexpression of AXL leads to drug resistance in some tumors [6].

3. BAX: [BCL2 ASSOCIATED X] CHROMOSOME 19; 19q13.33

The Bax gene is part of the Bcl-2 gene family. The Bax gene produces the protein, which is the proapoptotic protein that induces programmed cell death. The Bax gene induces the release of mitochondrial cytochrome c into the cytosol and activates the caspase pathway. Overexpression of cells leads to sudden cell death. And also, overexpression of the Bax gene induces apoptosis in a wide variety of cancer cells. Like the binary adenoviral vector system, gene therapy causes high levels of Bax and apoptosis in human pancreatic cancer cells [7]. The frameshift mutations in the BAX gene in the colon and gastric cancers of the MMP [microsatellite mutator phenotype] suggest that the inactivation of BAX during tumorigenesis may contribute to tumor progression by enhancing escape from apoptosis. BAX mutations are indicators of poor prognosis for both colon and gastric cancer of the MMP [8]. The Bax gene is a transcriptional target of p53.

And the p53 mutant was unable to activate Bax transcription. Bax protein heterodimerizes with Bcl-2 protein and neutralizes the anti-apoptotic function of Bcl-2. Decreased Bax an expression that leads to an increase in the Bcl-2/Bax ratio may inhibit apoptosis [9].

4. BCL2L12: [BCL-2 LIKE PROTEIN 12] CHROMOSOME 19; 19q13.33

The Bcl2L12 gene belongs to the BCL-2 oncogene family, which has cytoplasmic and nuclear anti-apoptotic activities and plays as an inhibitor of the tumor suppressor property of p53. Bcl2L12 occupies both the cytoplasm and nucleus. In the cytoplasm, Bcl2L12 inhibits caspases 3 and 7. In the nucleus, Bcl2L12 forms a composite with p53, likely reduces p53 protein stability, and prevents its attachment to selected target gene promoters [*e.g.*, p21, DR5, Noxa, and PUMA], thereby inhibiting p53-directed transcriptomic alters upon DNA damage [10]. Bcl2L12 induces an oncoprotein called β-crystalline, enabling Bcl2L12 to stop the activation of both caspase three and caspase 7 through the diverse mechanism and contribute to GBM [Glioblastoma multiform] pathogenesis and its biological properties [11].

5. BCL3: [B-CELL LYMPHOMA 3] CHROMOSOME 19; 19q13.32

BCL3 gene is encoded with B-cell chronic lymphatic chronic protein 3. BCL3 is a proto-oncogene candidate and was first found in a patient with chronic lymphocyte leukemia. BCL3 protein is one of the members of the IkB family, and increased BCL3 expression results in increased cell proliferation, survival, and malignant potential. BCL3 is also highly expressed in cutaneous T-cell lymphoma [12]. BCL3 is the cofactor of inflammatory mediator NF-kB, and it is dependent on Stat3 in mammary epithelial cells. A cell-autonomous disease-modifying role for Bcl3 *in-vivo*, affecting metastatic disease progression rather than primary tumor growth [13]. Bind NF-kB homodimeric complex of p50 or p52, which switches the transcriptional properties of the homodimers from a repressive to an activating state. The mRNA and protein levels of BCL3 have been overexpressed in breast cancer, nasopharyngeal carcinoma, endometrial cancer, hepatocellular carcinoma, and colorectal cancer. BCL3 promoted proliferation and cell cycle progression in Colorectal cancer, and STAT3 was recognized as a direct functional mediator of BCL3 in CC [14].

6. BRD4: [BROMODOMAIN-CONTAINING PROTEIN 4] CHROMOSOME 19; 19p13.12

BRD4 gene is encoded with the protein called Bromodomain-containing protein 4. BRD4 is a member of the Bromodomain and extra terminal domain [BET] family. BRD4 is the nuclear protein that plays a significant role in maintaining

CHAPTER 8

Chromosome 20

Harini Hariharan[1], Abhishek Mitra[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: Over the years, many scientists and doctors have been treating the deadly disease of cancer but are not able to find a permanent treatment for this disease. Also, sometimes it becomes very difficult 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 undergoing, which is causing cancer to progress, and know 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 mostly 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 alterations 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 20, are related to different types of cancer.

Keywords: Amplification, Cancer, Chemotherapy, Chromosome 20, Chromosome Rearrangements, Duplication, Gene Duplication, Mutation, Oncogene, Proto-Oncogene.

[*] **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

1. GENE -TNFRSF6B; TNF RECEPTOR SUPERFAMILY MEMBER 6B LOCATION -20q13.33

The Protein TNFRSF6B is coded by TNFRSF6B-gene and has been showcased to amplify and overexpress the proteins, which has been detected in a variety range of cancers and later considered as a chemo-resistance prognosticative-factor in a few studies. It was demonstrated that the protein TNFRSF6B-DCR3 attaches to ligand FAS-L, inhibiting FAS-L-induced apoptosis. The TNFRSF6B gene amplified protein was detected from a study of 35 colon and lung tumors, thus hypothesizing the fact that tumor cells may get away from FASL-dependent immune cytotoxic strike by regulating the decoy-receptor that inhibits and blocks the FASL. Incorrect splicing caused by extensive alternations is one of the molecular indicators for various mammalian tumors. For example, alternate transcripts of soluble-guanylyl cyclase, which is also known as an obligatory heterodimer formed due to incorrect splicing, are found in malignant and benign breast cancers [1]. Other examples include TGF-β and DcR3, which also result from extensive alterations in splicing; these are now a few important unique drug targets for breast-tumor immunotherapy, as it was observed in 57.7% of patients, suffering from breast cancer overexpressed these two molecules [2]. Study analysis on HCC showed the importance of miR340 as it plays a pivotal mechanism in the activation and regulation of cancer deterioration and occurrence when the DcR3-gene is indulged in tumor cell apoptosis and proliferation [3].

2. GENE -PCNA; PROLIFERATING CELL-NUCLEAR ANTIGEN. LOCATION -20p12.3

PCNA gene is known as a DNA clamp and actuates as a co-factor for DNA-polymerase δ, thus playing an essential role in DNA replication in eukaryotes. The PCNA gene is a homo-trimer, and it functions as a scaffold framework to enroll proteins indulged in DNA repair, DNA replication, epigenetics, and chromatin remodeling. When DNA damage response (DDR) is triggered, this protein undergoes ubiquitination to get involved in the RAD6-dependent DNA repair pathway.

It was observed from different studies that there was a specific increase in the level of TCTN1 expression due to the presence of miR-216a-5p in ESCC tissues [4]. From these studies, only other genes, like PCNA, FOS, *etc*., were also thought to be responsible for the increased level of the PPI network [5].

3. GENE -GNAS; GNAS COMPLEX LOCUS LOCATION -20q13.32

GNAS, an α Stimulating-polypeptide, is a locus present on chromosome 20's q arm. Its main function is to form a highly specific protein sub-unit, hetero-trimeric

G protein α-subunit Gs-α, which is the important component of GPCR-activated adenylyl-cyclase signal-transduction pathways. It demonstrated in various studies that alterations in the GNAS gene have resulted in many conditions, which include pseudohypoparathyroidism-type1B, Albright-hereditary osteodystrophy, McCune-Albright syndrome, pseu-dohypopa-rathyroidism-type 1A, polyostotic fibrous-dysplasia of bones, progressive osseous-heteroplasia, and few pituitary cancers [6]. Also, somatic mutations in GNAS is identified in ovarian cysts, adrenal hyperplasia, adrenocortical, kidney tumor, thyroid carcinoma, Leydig cell cancer, and pituitary tumors [7].

4. GENE -SS18L1; SS18L1 SUBUNIT OF BAF CHROMATIN RE-MODELING COMPLEX.LOCATION -20q13.33

SS18L1 gene encodes an important subunit of the chromatin-remodeling complex, which is neuron-specific, thus, the mutation of this particular gene is responsible for ALS [amyotrophic lateral sclerosis]. Certain specific SS18-SSX gene fusions and variable epithelial differentiation are characters of synovial sarcoma as it was analyzed from SS18 FISH assay, and it also revealed novel fusions like EWSR1-SSX, SS18L1-SSX and SS18-SSX [8]. These specific rare fusions were proved by using techniques like RT-PCR and Sanger sequencing [9]. The analysis of this novel subset of SS18 FISH was done by means of MABs and RNA-sequencing that identifies SSX C-terminus and SSX-SS18 [10].

5. GENE -ASXL1; ASXL-TRANSCRIPTIONAL REGULATOR 1. LOCATION -20 q11.21

The gene ASXL1 is responsible for encoding chromatin-binding protein which is required for identifying the segment recognition in the growing embryo and the protein encoded by this gene disrupts the chromatin structure in localized regions, which in turn enhances the transcription of specific genes while suppressing the transcription activity of another gene, the protein coded by ASXL1 also actuates as a ligand-dependent coactivator for RA receptor. For diseases, for example, myelodysplastic syndromes and chronic myelomonocytic leukemia, there's a record that this gene was mutated [11]. In a deubiquitinase complex, ASXL1 is the regulatory subunit, while BAP1 is the catalytic subunit. The heterozygous alterations of the ASXL1 gene result in pre-mature shortening and are predominantly found in Bohring Opitz syndrome and myeloid leukemia [12]. It's observed that regulation of shortened hyper-active BAP1-ASXL1 complexes in cancer cell lines out turned in H3K27me3 depletion, mast cell-lineage spontaneous-differentiation, and H2AK119Ub removal. BM (bone marrow) precursor analysis showed that regulation of the BAP1-ASXL1 complex may lead to hyper-elevated differentiation of myeloid lineage [13].

CHAPTER 9

Chromosome 21

Thilaga Thirugnanam[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: The significance of human chromosome 21 is that the trisomy of human chromosome 21 causes Down syndrome in children. There are about 235 protein-coding genes on chromosome 21. Mutations like translocation in human chromosome 21 cause different conditions such as partial monosomy 21, core binding factor acute myeloid leukemia, ring chromosome 21, and other types of cancers such as acute lymphoblastic leukemia. Mutation in the *DSCAM* gene causes mental retardation and facial deformities in down syndrome. The human chromosome 21 also comprises the *APP* gene, where the expression of the gene causes Alzheimer's disease. The genes that are involved in causing Down syndrome and Alzheimer's diseases are also involved in cancer. This chapter discusses 63 genes of human chromosome 21 that are involved in different types of cancer.

Keywords: APP, BACH1, BAGE, Cancer, Down syndrome, ETS2, Leukemia, Metastasis, RUNX1, Tumor.

1. ADAMTS1 – ADAM METALLOPEPTIDASE WITH THROMBOSPONDIN TYPE 1 MOTIF1 CHROMOSOME 21; 21q21.3

ADAMTS1 gene belongs to a family of extracellular protease groups which is required in the extracellular microenvironment [1]. It plays a significant role in regulating ancillary domains, glycosylation, and processing propeptide [1]. The absence of *ADAMTS1* resulted in a pro-inflammatory response by affecting lymphocytes and myeloid cells in the bone marrow and spleen [2]. This corresponds to the blocking potential of ADAMTS1 of tumors, indicating that this gene is essential for modulating immune response [2]. ADAMTS1 is first identified to be expressed in cachexigenic colon cancer cells [3]. The *in vivo* study on ADAMTS1 showed that overexpression of the *ADAMTS1* gene might lead to mammary tumor growth and metastasis progression, showing that it can be a potential therapeutic target to suppress metastatic breast cancer [3].

[*] **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

2. ADARB1 - ADENOSINE DEAMINASE RNA SPECIFIC B1 CHROMOSOME 21; 21q22.3

ADARB1 is an RNA editing enzyme where it changes adenosine to inosine [A-to-I] [4]. Various studies have reported the involvement of the *ADARB1* gene in different cancers. In metastatic lung adenocarcinoma, the *ADARB1* gene is expressed in lower levels, leading to the inhibition of metastasis [4] and acting as a tumor suppressor in lung cancer [5]. Also, a recurrent genetic loss at the *ADARB1* locus has been found in non- small cell lung cancer [5]. *ADARB1 is* also downregulated in lung squamous cell carcinoma, which is different from lung adenocarcinoma according to Growth Expression Omnibus [6]. Expression of *ADARB1* results in less price-miRNA processing in chronic lymphocytic leukemia, but the processing efficiency is recovered as it is localized in the nucleus [7]. Another study showed that *ADARB1,* along with other epigenetics-related genes, are upregulated in moderately differentiated tumors of prostate cancer [8].

3. AIRE - AUTOIMMUNE REGULATOR CHROMOSOME 21; 21q22.3

The autoimmune regulator or *AIRE* gene, a transcription factor involved in the tolerance process, encodes antigens in specific tissues such as medullary thymic epithelial cells [9]. In breast cancer cells, the AIRE gene is expressed abnormally, which is related to good prognosis [9]. In skin tumor keratinocytes, the *AIRE* gene stimulates the transcription of the *K17* gene resulting in tumorigenesis or acute inflammation [10]. Another study in tumor-associated regulated T cells indicates the role of AIRE in the growth of tumor-associated Foxp3-positive regulatory T cells [11]. *AIRE* upregulation is observed in oral squamous cell carcinoma leading to the expression of a few cancer-related genes [12]. The alleles of *AIRE* single nucleotide polymorphisms are suspected to be involved in melanoma by changing melanoma-specific T cell repertoire [13]. *AIRE* gene is also expressed in osteosarcoma [14]. A study using a mouse model showed that the *AIRE* gene might be an important factor to promote prostate cancer progression [15].

4. APP - AMYLOID BETA PRECURSOR PROTEIN CHROMOSOME 21; 21q21.3

Amyloid beta precursor protein or APP, located across the cell membrane, is expressed in patients with Alzheimer's disease and forms amyloid plaque [16]. *APP* gene is induced by androgens which stimulate the proliferation of breast carcinoma cells and could act as a prognostic factor [16]. A pathway mediated by

the *APP* gene is required for prostate cancer growth in an androgen-dependent manner [17]. A study observed that phosphorylated APP expression is elevated in non-small cell lung carcinoma [18]. A study in squamous lung cancer cell lines observed that these cells secreted APPs [19]. In bladder tissues of cancer, the expression of *APP* is increased, leading to invasion, cell cycle, migration, and proliferation in the bladder [20]. Overexpression of *APP* is observed in recurrent nasopharyngeal carcinoma and might be considered a potential biomarker [21].

5. B3GALT5 - BETA-1, 3 -GALACTOSYLTRANSFERASE 5 CHROMOSOME 21; 21q22.2

B3GALT5 is an enzyme that overexpresses and leads to the interaction of cancer-related globo - series GSL complex in breast cancer cells [22]. Apart from breast cancer, long noncoding *B3GALT5* antisense RNA 1 has been observed in gastric cancer, where it is expressed in higher amounts [23]. This serves as a biomarker for the diagnosis of gastric cancer [23]. These long noncoding RNAs also play a significant role in colon cancer liver metastasis in which the expression of *B3GALT5* antisense RNA 1 is reduced [24]. B3GALT5, along with a membrane protein expressed in higher quantities in hepatocellular carcinoma, provides insight into the recurrence and overall survival of hepatocellular carcinoma [25].

6. BACH1 - BTB DOMAIN AND CNC HOMOLOG 1 CHROMOSOME 21; 21q21.3

The *BACH1* gene is involved in myriad cancers. Overexpression of *BACH1* in breast cancer cells, along with a transcription factor, HMGA2, suppresses abnormal cellular events such as migration, apoptosis, evasion, proliferation, and clonogenicity [26]. *BACH1,* along with a long noncoding RNA, *MALTA1* expressed together in higher amounts in triple-negative breast cells and might be used as biomarkers [27]. In a human ovarian cancer cell, *BACH1* has increased the expression of epithelial-mesenchymal transition genes in slugs and snails and also it recruits HMGA2, leading to cell migration [28]. Apart from these, BACH1 plays a significant role in other cancers, such as lung cancer metastasis [29], colorectal cancer [30], pancreatic cancer [31], prostate cancer [32], and pancreatic cancer metastasis [33]. BACH1 also has a therapeutic potential, like a combination therapy in breast cancer [34].

7. BAGE - B MELANOMA ANTIGEN CHROMOSOME 21; 21q11.1

BAGE or *BAGE1* gene was first identified in human melanomas, which encodes an antigen and is recognized by Cytolytic T lymphocytes [35]. BAGE, along with few other tumor-associated antigens were dysregulated in non-small cell lung

CHAPTER 10

Chromosome 22

Sayooj Madhusoodanan[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: When the collection of human Chromosome 22 was first suggested in 1999, it became the most extended, non-stop stretch of DNA ever decoded and assembled. Chromosome 22 became the first of the 23 human chromosomes to decode due to its minimal length and affiliation with numerous diseases. Chromosome 22 involves several genes that contribute to cancer genetics in one way or the other. The contribution of chromosome 22 in abnormalities is evident through somatic translocations, germline and somatic, and in certain cases, overexpression of genes. One famous example is the Philadelphia translocation, particularly in chronic myeloid leukemia cells. Various gene contributions about types of cancer such as Acute Myeloid Leukemia, colorectal, lung, breast cancer and many more have been reported in studies related to chromosome 22. This chapter takes a run-through of important targeted studies of a gene that facilitates itself as a part of cancer genetics.

Keywords: Chromatin modeling, Heterodimerization, Intercellular stress, Metastasis, Molecular aberration, Philadelphia chromosome, Pro-apoptotic, Prognosticative marker, Polymorphisms, Tumor migration.

1. ATF4: ACTIVATING TRANSCRIPTION FACTOR 4. CHROMOSOME 22; 22q13.1

ATF4 gene is associated with coding transcription factors belonging to the family DNA binding protein having the property to bind to a tax-responsive enhancer element [1]. The involvement of *ATF4* happens in many intracellular stress pathways [2]. In human cancer cells, ATF4 has been identified to be expressed ubiquitously for cellular proliferation. The pathways in which *ATF4* plays a role are hypoxia, oxidative and endoplasmic reticulum stress, where in tumor-spotted areas, expression of *ATF4* was recognized in the hypoxic and nutrient-deprived region [2 - 4]. The ability of *ATF4* to promote homeostasis along with cancer cell

[*] **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

survival through the regulation of amino acid biosynthesis, autophagy, and angiogenesis makes *ATF4* an interesting target for therapeutic associations in various cancer types [5].

2. BCR: BREAKPOINT CLUSTER REGION PROTEIN. CHROMOSOME 22; 22q11.3

The BCR gene is widely recognized for its association with the Philadelphia chromosome (PH), which is an abnormally short chromosome 22, including the chimeric association of the ABL gene from the 9th chromosome that causes PH+ leukemias. The *BCR-ABL* chimeric gene is now recognized in the class of fusion genes [6]. The functional characteristics of this gene include Kinase activation for the facilitation of cell growth and signaling, interaction with Ras-related pathways, and Ship proteins. Other involvements include the effect of the gene in apoptosis, *Stat5* and adhesion molecules [7] (Fig. **1**).

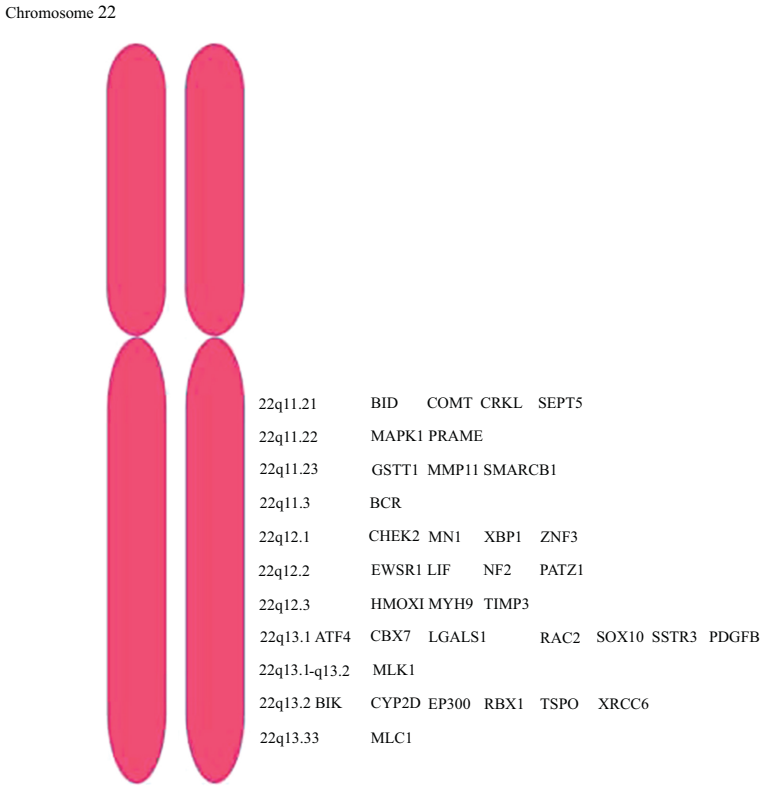


Fig. (1). This figure displays the loci of the genes from Chromosome 22 whose roles in cancer have been explained in this chapter. Sayooj Madhusoodanan designs this diagram.

3. BID: BH3 INTERACTING DOMAIN DEATH AGONIST. CHROMOSOME 22; 22q11.21

The *BID* gene (Fig. **1**) is said to be responsible for the encoding of death agonists, having the potential for heterodimerization with an agonist (*BAX*) or an antagonist (*BCL2*). *BID* is a pro-apoptotic gene and is widely linked to gastric cancer [8, 9]. The involvement of the gene associated with the apoptotic process and *BCL-2* makes it an important target for cancer and programmed cell death studies [10, 11].

4. BIK: BCL-2 INTERACTING KILLER. CHROMOSOME 22; 22q13.2

BIK gene (Fig. **1**) is a pro-apoptotic gene encoding protein that shares the BH3 domain with other apoptotic-related genes such as *BAX, BID, BAK,* and *BAD* [12]. *BIK* is said to be involved in breast cancers and colorectal cancers. The functionality of the BIK protein includes the formation of heterodimers with anti-apoptotic proteins and the hindrance of antiapoptotic protein functions [13, 14]. BIK also induces or triggers apoptosis through the P53-independent pathway. *BIK* mutations have also been reported in lymphomas [15].

5. CBX7: CHROMEBOX 7. CHROMOSOME 22; 22q13.1

CBX7 is responsible for the protein-coding that includes the Chromatin organization modifier domain, a component of poly-comb repressive complex playing an essential role in the life span of several cells. In human cancers, the encoded protein is downregulated, and the carcinogenesis involvement is still under study. Currently, *CBX7* is known as a Tumor suppressor playing a vital role in the pathogenesis of cancer [16]. The correlation of *CBX7* expression has been associated with malignant thyroid cancer [17]. The loss of *CBX7* causes aggression in the phenotypes of pancreatic [18], colon [19], and gastric cancer [20]. *CBX7* also has the functionality to modulate the expression of certain specific effector genes, which are critical in advanced stages of carcinogenesis [21].

6. CHEK2: CHECKPOINT KINASE 2. CHROMOSOME 22; 22q12.1

CHEK2 encodes a protein that is a putative Tumor suppressor as well as a cell cycle checkpoint regulator. Activation of the protein has been shown to stabilize *p53* facilitating cell cycle arrest in the G1 phase. *CHECK2* mutations have been

CHAPTER 11

Chromosome X

Anusha Mandem[1], Saurav Panicker[1], Abhishek Mitra[1] and **Satish Ramalingam[1,*]**

[1] *Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India*

Abstract: X Chromosome is the sex chromosome that is found in many organisms. Both males and females, including mammalians, have X Chromosomes. Females have XX sets of chromosomes, and males have XY sets of chromosomes. X Chromosome aids in identifying the sex of the organism. The Human X chromosome contains approximately 1500 genes. These genes may undergo some genetic alterations and eventually lead to complex diseases. Genetic mutations in some of the genes of the X chromosome are associated with cancer. Some specific mutations are observed in human cancer cells. This chapter specifically relayed on X chromosomal genes that are associated with different types of cancer and gave information on the location of the gene in the X chromosome. Moreover, the function of the specific gene and information regarding how many types of cancers were associated with a particular gene, has also been provided.

Keywords: Ceruloplasmin, Chromosome Condensation, Chromosome Fragmentation, Cowchock Syndrome, Hepatocellular Carcinoma, Leiomyomatosis, Malignant, Microtubule, Ovarian Cancers, Recessive, Simpson Dysmorphia, X-linked.

1. AGTR2 - ANGIOTENSIN II RECEPTOR TYPE 2 CHROMOSOME X; Xq23

The protein encoded by this gene belongs to the G-protein coupled receptor 1 family, and functions as a receptor for angiotensin II [1]. It is an integral membrane protein that is highly expressed in the fetus, but scantily in adult tissues, except the brain, adrenal medulla, and atretic ovary [1]. This receptor has been shown to mediate programmed cell death, and this apoptotic function may play an important role in developmental biology and pathophysiology. Angiotensin II [AII], the biologically active effector of the renin-angiotensin system, is a

* **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

major regulator of blood pressure and electrolyte balance and a growth factor for diverse cell types [1]. AII exerts its physiological effects by interacting with two pharmacologically distinct subtypes of receptors, designated AT{sub-1}, and AT{sub-2} [1]. Most of the known responses to AII are mediated by the AT {sub-1} subtype. AT{sub-2} receptor may play a most important role in processes involving cellular growth and differentiation [1]. Moreover, AT {sub 2} receptor expression is enhanced in the adult in wound healing, in the neointima of injured vessels, and in pheochromocytoma [1]. Angiotensin-II [A-II] type 2 receptor [AGTR2] seems to be involved in different types of cancer [2]. AGTR2 specifically has its role in oral squamous cell carcinoma [OSCC] [2]. In OSCC cell lines, intracellular angiotensin-II was produced by themselves. Notably, losartan, an angiotensin receptor blocker, inhibited intracellular angiotensin-II production and AGTR2 nuclear localization to enhance the antitumoral effect of 5-FU in an OSCC tumor model [2].

2. BCOR - BCL-6 COREPRESSOR CHROMOSOME X; Xp11.4

The protein encoded by this gene was identified as an interacting corepressor of BCL6, a POZ/zinc finger transcription repressor that is required for the germinal center formation and may influence apoptosis Germline mutations in the *BCL6 Co-Repressor [BCOR]* gene, situated at Xq27-28, are associated with two overlapping X-linked dominant disorders, the Oculo-facio-cardio-dental [OFCD] syndrome and syndromic microphthalmia [3]. In addition, somatic mutations in *BCOR* were described within the last few years in adults and children with AML, particularly in cases arising in the context of aplastic anemia and in patients with antecedent myelodysplastic syndromes [3]. *BCOR* encodes a ubiquitously expressed protein that is involved in BCL6-mediated transcriptional repression [3]. Clear cell sarcoma of the kidney [CCSK] is a rare pediatric renal malignant tumor [4]. The majority of CCSKs have internal tandem duplications [ITDs] of the *BCOR* gene [4].

3. CD99 - CLUSTER OF DIFFERENTIATION 99 CHROMOSOME X; Xp22.33

CD99 antigen [Cluster of differentiation 99], also known as MIC2 or single-chain type-1 glycoprotein, is a heavily O-glycosylated transmembrane protein that is encoded by the *CD99* gene in humans [5]. CD99 is characteristically expressed in Ewing's sarcoma/primitive neuroectodermal tumor [5]. The CD99 expression was usually seen in the intestinal type adenocarcinoma, while rarely in the diffuse type [5]. CD99 expressed in non-neoplastic gastric mucosa and gastric adenocarcinomas and its downregulation in gastric adenocarcinoma may be associated

with cellular dedifferentiation and/or MMP-2 overexpression [5]. Src and focal adhesion kinase mediates the intracellular signaling pathway of a CD99 splice variant for the induction of motility of human breast cancer cells [6].

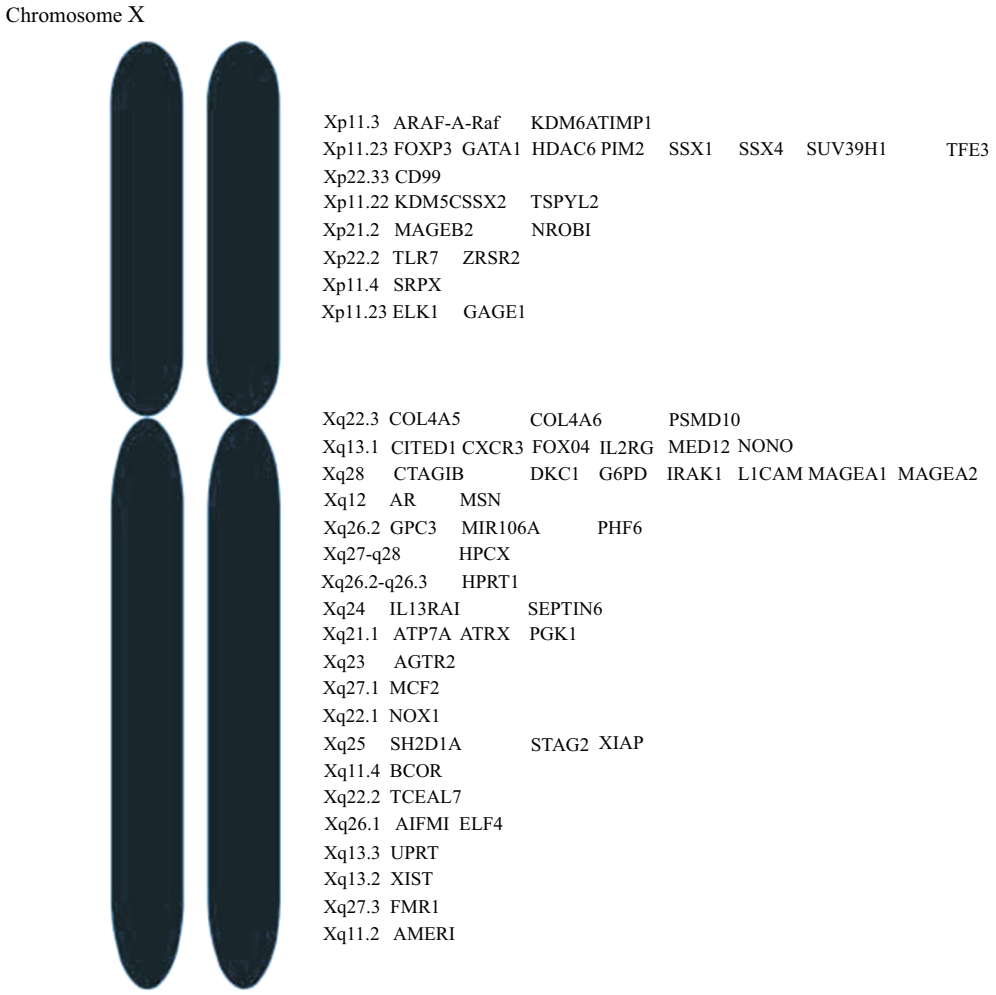


Fig. (1). This figure displays the loci of the genes from Chromosome X whose roles in cancer have been explained in this chapter. Sayooj Madhusoodanan designs this diagram.

4. AIFM1 - APOPTOSIS-INDUCING FACTOR MITOCHONDRIA ASSOCIATED 1 CHROMOSOME X; Xq26.1

This gene (Fig. **1**) encodes a flavoprotein essential for nuclear disassembly in apoptotic cells, and it is found in the mitochondrial intermembrane space in healthy cells [7]. Induction of apoptosis results in the translocation of this protein

CHAPTER 12

Chromosome Y

Sowmiya Sattanathan[1], Saurav Panicker[1] and **Satish Ramalingam[1,*]**

[1] Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India

Abstract: Sex chromosome constitution vary genetically in both genders, such as XY in male and XX in female. Even though the chromosomes X and Y advanced from the autosomal pair of the same ancestor, male-specific genes were harbored by the Y chromosome. This Y chromosome plays a crucial role in germ cell differentiation, sex determination in males, and numerous tissue masculinization. Translocations or deletions of SRY, the sex-determining gene of the Y chromosome, enable sex development disorders with dysgenic gonads. Gonadal improvement failure outturns not only in infertility but also in the highest possibilities of GCT (Germ Cell Tumour), like various kinds of testicular GCT and gonad blastoma. Studies have shown that selected somatic cancers are closely related to both losses of Y chromosome genes, ectopic expression, or Y chromosome. These observations remark that genes of the Y chromosome are associated with male diseases and health more than attic turns out not only in infertility but also in the highest possibilities of GCT (Germ Cell Tumour) like various kindspated. Even though only a compact amount of protein-coding genes are seen in Y chromosomes male-specific region, the effects of those Y chromosomal genes on human disease are still predominantly unknown. In this part, we can find the participation of selected genes of the Y chromosome in cancer growth in men.

Keywords: Chromosome Y, Gonads, Male fertility, Melatonin, Prostate cancer, Sex chromosome, SRY, Tumor, Ubiquitin.

1. AMELY -AMELOGENIN Y-LINKED CHROMOSOME Y; Yp11.2

An AMELY-coupled has upstream positive regulation of immune response formulated protein secretion to Wnt signaling and calcium into cytosol-induced regulation of cell growth and angiogenesis [1]. This process has been taking place in human hepatocellular carcinoma. *AMELY* has been identified to be one of the highly expressed genes in human HCC [1].

[*] **Corresponding author Satish Ramalingam:** Department of Genetic Engineering, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, India; E-mail: rsatish76@gmail.com

2. ANT3 -ADENINE NUCLEOTIDE TRANSLOCATOR 3 CHROMOSOME Y; Yp11.2

ANT3 [Adenine Nucleotide Translocator 3] is a translocase gene, and this gene is placed on the pseudoautosomal region of both X and Y chromosomes, also *ANT3* gene is not engaged in the X inactivation process [2]. In PC3 [Prostate Cancer Cell line], the outcome of the *ANT3* gene has been seen with the help of PCR amplification [3].

3. ASMT -ACETYLSEROTONIN O-METHYLTRANSFERASE CHROMOSOME Y; Yp-11.2

N-Acetylserotonin O-methyltransferase, also known as ASMT, is an enzyme that catalyzes the final reaction in melatonin biosynthesis: converting Normelatonin to melatonin [4]. *ASMT* or acetylserotonin O-methyltransferase [[human]] Low HIOMT expression is associated with lung cancer [4]. This gene belongs to the methyltransferase superfamily and is located in the pseudoautosomal region [PAR] at the end of the short arms of the X and Y chromosomes [4]. The encoded enzyme catalyzes the final reaction in the synthesis of melatonin and is abundant in the pineal gland. Alternatively, spliced transcript variants have been noted for this gene [4].

4. AZFC -AZOOSPERMIA FACTOR C REGION CHROMOSOME Y; Yq11

AZFc is Azoospermia factor c region, deletion at this region leads to infertility [5]. Specifically, there is a part of AZFc known as gr/gr [5]. The deletion of gr/gr is related to infertility [5]. Also, this deletion of gr/gr is strongly related to seminoma compared with non-seminoma in TGCT [5]. Testicular germ cell tumor [TGCT] is a tumor that is common in young men [5].

5. BPY1 -BASIC PROTEIN Y 1 CHROMOSOME Y; Yq11.2

BPY1 [Basic Protein Y 1] gene is present on the Y chromosome [6]. *BPY1* gene cipher basic protein of Y-chromosome mediated and testis-specific [6]. The role of *BPY1* is not known, but its expression is seen in the human testis [6]. There is an identical loss of Y-chromosome-specified genes in prostate cancer [6]. The deletion of the *BPY1* gene ensures prostate cancer [6]. The loss of the *BPY1* gene [Yq11.2] was shown in 14% of cases [7 of 50]. It was lost in prostate cancer samples [6].

6. BPY2 -BASIC PROTEIN Y 2 CHROMOSOME Y; Yq12.1

BPY2 found on the Y chromosome, interconnects with ubiquitin protein ligase E3A, which is involved in male germ cell development and infertility [7]. *BPY2* gene correlates with high expression in prostate cancer on the Y chromosome [7]. This gene is linked with cell growth and may contribute to tumor progression and metastasis [7]. BPY2 are common proteins that are Y-chromosome mediated and testis-specific. *BPY2* gene was lost in 42% of prostate cancer samples [21 of 50] [6].

7. CD99 -CLUSTER OF DIFFERENTIATION 99 CHROMOSOME Y; Yp11.2

CD99 gene is located in the pseudoautosomal region [PAR] and is present at the edge of the short arm on both x and y chromosomes [8]. This *CD99* gene correlated with spontaneous rosette development together with erythrocytes. *CD99* gene is 32KD, with the association of T cell surface glycoprotein [8]. The SVM model analysis gives that with at least 95% of precision, the *CD99* gene is sincerely involved in prostate cancer [9].

8. CDY1 -CHROMODOMAIN PROTEIN, Y-LINKED, 1 CHROMOSOME Y; Yq11.23

CDY1 [Chromodomain Protein, Y-Linked, 1] has been involved in histone modification with the help of its chromodomain and catalytic domain [10]. It is believed that CDYL gives rise to CDY1 because CDY homology is not found in mice [10]. The deletion of the *CDY1* [Chromodomain Protein, Y-Linked, 1] gene may raise the risk of seminoma [11].

9. CRLF2 -CYTOKINE RECEPTOR-LIKE FACTOR 2 CHROMOSOME Y; Yp11.2

Increased *CRLF2* expression is associated with *JAK2* mutation, a combination that transforms hematopoietic cells, suggesting that mutant *JAK2* and *CRLF2* may cooperate to contribute to B-ALL formation [12]. Importantly, elevated *CRLF2* expression correlates with poor outcomes in high-risk B-ALL patients [12]. This gene encodes a member of the type I cytokine receptor family [13]. *CRLF2* was associated with the activation of the JAK-STAT pathway in cell lines and transdu-

SUBJECT INDEX

A

B

C

D

E

G

H

I

L

M

N

O

P

R

S

T

U

V

W