Journal of Data Science **11**(2013), 673-714

Sequence Mutations of Genes Pertaining to Malignancy in Cancer

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Abstract: Cancer is a complex disease where various types of molecular aberrations drive the development and progression of malignancies. Among the diverse molecular aberrations, inherited and somatic mutations on DNA sequences are considered as major drivers for oncogenesis. The complexity of somatic alterations is revealed from large-scale investigations of cancer genomes and robust methods for interring the function of genes. In this review, we will describe sequence mutations of several cancer-related genes and discuss their functional implications in cancer. In addition, we will introduce the on-line resources for accessing and analyzing sequence mutations in cancer. We will also provide an overview of the statistical and computational approaches and future prospects to conduct comprehensive analyses of the somatic alterations in cancer genomes.

Key words: Cancer, cancer databases, mutations.

1. Introduction

Cancer cells harbor a large number of molecular aberrations. At DNA levels the sequence contents, copy numbers and epigenetic states of many genes and non-coding regions undergo abnormal changes. At RNA levels many mRNAs and microRNAs are differentially expressed or possess abnormal splice forms. At protein levels the expressions, activities and functions of proteins may also change. These alterations perturb the gene regulatory networks and thus empower cells with capacities for malignancy such as perpetual replication, abrogation of apoptosis, potential for metastasis and drug resistance. Information about these aberrations provides a molecular basis to understand the mechanisms of tumorigenesis and develop prognosis and treatment technologies of cancer.

Among the various molecular aberrations, mutations on DNA sequences are considered as the most upstream and major driving events for oncogenesis. Base

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substitutions may alter the structures and functions of proteins, introduce early stop codons in RNA synthesis, or affect transcription factor bindings on promoters. In addition, insertions and deletions of DNA fragments may add/remove amino acid residues of encoded proteins, change reading frames and disrupt RNA synthesis, as well as amplify or delete transcription factor binding sites (see definition of mutation types from Figure 1). Decades of cancer studies prior to the post-genomic era have accumulated substantial knowledge regarding the sequence mutations of well-known oncogenes and tumor suppressors. The functional and mechanistic consequences of sequence mutations on a few genes such as *TP53* and *TP16* are thoroughly documented. However, the biological implications of most sequence mutations or variations remain unclear. These variations include the genomic alterations that cause or promote cancers (drivers) and the alterations that are present in the cancer genomes but do not contribute to carcinogenesis (passengers) (Davies *et al.*, 2005). Separation of the driver mutations responsible for clinical phenotypes from the vast number of passenger mutations is a leading question of cancer genomics today.

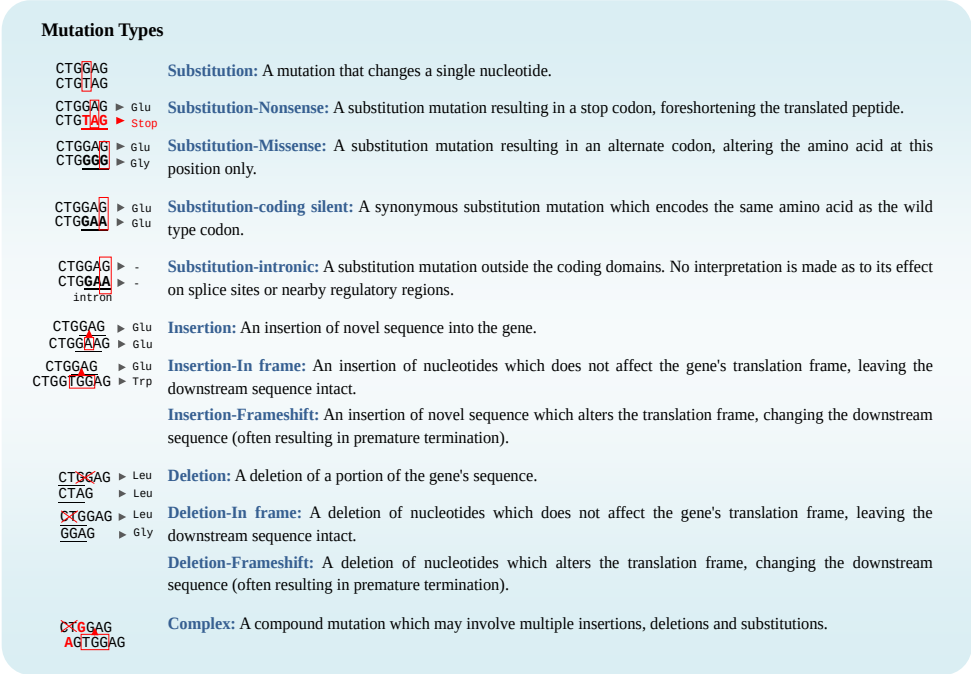

Figure 1: Mutation type and definition

2. Somatic Mutations and Their Implications in Cancer

As a central driving cause of tumorigenesis, somatic mutations have been

broadly documented. Alterations on protein coding or regulatory regions of the genome potentially disturb or enhance the normal functions of a gene, and these changes may be transmitted to descendants through a lineage of reproductive cells (Knudso, 2001). Some genetic alterations are confined to local regions or single genes. These include missense or nonsense base substitutes, insertions and deletions that lead to frameshift (Lewin, 2004). Other alterations may affect large genomic regions such as rearranged chromosomal segments and copy number variations (Edmunds, 2008).

In cancer, somatic mutations can arise in the genomes of dividing cells during DNA replication. Genetic modifications exhibit diverse patterns in different cancers. Some cancer genomes contain more than 100,000 mutations, whereas the others may carry less than 1,000 mutations (Greenman *et al.*, 2007; Wood *et al.*, 2007; Sjöblom *et al.*, 2006; Stephens *et al.*, 2005). The functions of most of these mutated genes possess one or multiple "hallmarks" of cancer (Hanahan and Weinberg, 2011). The hallmarks include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. First, cancer cells constantly fire proliferative signals, while normal cells carefully control the production and release of growth-promoting signals through the cell cycle. Progression from one phase to the next phase of the cycle is controlled by a series of checkpoints. In cancer cells, the checkpoints are typically defective. Abnormal cell divisions can further destabilize cancer genomes and facilitate somatic mutations. Unrepaired/mutated DNA can enter cell cycles and result in an incorrect segregation of their chromosomes. The dysregulated proliferative signals are conveyed by growth factors, emitted via branched intracellular signaling pathways, and lead to malignancy. Second, cancer cells typically block or suppress anti-growth signals through cell cycle regulation. In normal cells, growth factor signals are antagonized by cellular conditions such as cell sizes, DNA damage, and deficiency of nutrients or oxygen. In cancer cells, some of the tumor suppressor genes controlling anti-growth signals are mutated and thus dysfunctioning. Third, as another line of self-defense, abnormally dividing cells often trigger the mechanisms of programmed cell death (apoptosis). However, cancer cells typically harbor mutations on key genes of these mechanisms to evade apoptosis. Fourth, abnormally dividing cells escaping apoptosis still cannot replicate perpetually, as cell divisions will shorten the terminal ends of chromosomes (telomeres) and make the descendant cells become "aged". Cancer cells, however, are often capable of maintaining telomeres and thus preventing cell ageing. In addition to alterations within cancer cells, processes pertaining to interactions between cancer cells and the surrounding environment are also compromised. Some of the prominent processes altered include formation of new blood vessels (angiogenesis) to supply tumors with oxygen and nutrient, invasion to the surrounding tissue and migra-

tion to remote sites (metastasis), prevention of attack from the immune system, and chronic inflammation.

There are several ways to investigate the patterns of somatic mutations in distinct cancers. Some studies identified these patterns by estimating the rates of genomic rearrangement. For example, in colorectal and endometrial cancer, rates of single nucleotide changes and small insertions and/or deletions at polynucleotide fragments of MLH1 and MSH2 show increased values which can clearly define neoplastic changes (Vogelstein *et al.*, 1988; Lengauer *et al.*, 1998). Other phenotypic evidence such as erosion of telomeres can reveal mutated genes by capping the ends of chromosomes and provide an accumulation of numerous mutations with a high rate (Artandi and DePinho, 2010). However, some studies conflictingly suggested that only mutation rates of normal cells, without any phenotypic mutators, may be adequate for capturing the development in some cancers (Bodmer and Loeb, 2008; Loeb *et al.*, 2008).

Non-synonymous (missense, nonsense or frameshift) mutations can be responsible for cancer development and progression (Edmunds, 2008; Weinberg, 2007). However, only a small fraction of them called drivers actually cause tumors. The remaining mutations in cancer genomes are likely to be neutral and are not considered as a major cause in tumorigenesis. The term passengers is used to denote this type of mutation (Greenman *et al.*, 2007). In general, drivers compromise the process of cell maintenance by conferring a clonal growth advantage on cancer cells, but the passengers do not. Distinguishing driver from passenger mutations is a key challenge in cancer genomics for the strong implication in prognosis and treatment and the defining of functional information of most mutations (Greenman *et al.*, 2007; Ferrer-Costa *et al.*, 2005).

Several methods for classifying mutations as drivers or passengers are reported in Figure 1 and Table 1. The first fourteen rows of Table 1 are from Baudot *et al.* (2009). Since the drivers would affect protein functions, assessing the impact of mutations in conserved domains of a given protein is suggested. The prediction models based on sequences and/or protein structures were demonstrated through functionally neutral and deleterious amino acid changes (Yue *et al.*, 2006; Torkamani and Schork, 2007; Ferrer-Costa *et al.*, 2005). Several bioinformatics tools are used to prioritize candidate mutated genes. For instance, Ng and Henikoff (2003) developed SIFT (Sorting Intolerant From Tolerant) by using sequence homology between closely related protein species to measure effects of amino acid substitutions in protein-coding regions. Likewise, Clifford *et al.* (2004) developed the LogR.E-value algorithm to determine the difference between a wildtype and variant protein by measuring their fitness to a Pfam model. Kaminker *et al.* (2007b) developed CanPredict using known cancer-associated variants to build a general description of a cancer mutation. They combined SIFT, LogR.E and

gene ontology similarity score (GOSS) to measure the characteristics of a cancer mutation and classify variants as cancer or non-cancer. Ferrer-costa *et al.* (2005) developed a web-based tool called pMut for the annotation of pathological mutations on proteins. However, the prevalence and characteristics of drivers and passengers are not well defined. The structure-based models confirmed the passenger mutations but did not find any predicted driver mutations. Thus, other investigations were recommended. The ratio between non-synonymous and synonymous mutation rates (K_a/K_s rates) is commonly used to quantify the strength of natural selection in molecular evolution (Greenman *et al.*, 2007). Higher ratios can be remarked as a result of a positive selection driving oncogenesis. However, passenger mutations may have similar K_a/K_s ratios to driver mutations as they may also alter protein structures. Therefore, an alternative approach calculated the differences between observed and expected frequencies of non-synonymous mutations (Wood *et al.*, 2007; Sjöblom *et al.*, 2006). A gene with a higher frequency of observed mutations relative to the expected frequency was expected as a driver. Another approach to identify drivers focused on large homozygous deletions (HDs) of recessive cancer genes (Bignell *et al.*, 2010) such as *CDKN2A*, *RB1*, *SMAD4*, *SMARCB1*, *MAP2K* or *PTEN*. Yet, in addition of recessive cancer genes, HDs also appear on common fragile sites. A presence of inactivating mechanisms that occurs on fragile sites such as protein truncation have been applied to detect a number of HDs and their associated regions (Lukusa *et al.*, 2008). However, a limitation of these methods is a requirement of very large sample size. The insufficient samples would not meet the statistical thresholds. Furthermore, these statistical criteria do not provide information about the specific alleles such as point mutations that may affect epigenetic states. For example, a decreased vulnerability of C-to-T transition mutations can increase an efficiency of methylation in CpG sites and lead to gene silencing (Jones and Baylin, 2002). To address this drawback, genetic information such as related pathways and/or annotation of known cancer genes have been currently incorporated in analysis (Ekins *et al.*, 2007; Subramanian *et al.*, 2005; Redon *et al.*, 2006; Kaminker *et al.*, 2007a, Aerts *et al.*, 2006; Furney *et al.*, 2008).

In addition, although the total number of mutations in cancers is large, only a few genes such as *TP53* and *RB1* may have prevalent and recurrent mutations (Soussi, 2000; Valverde *et al.*, 2005; Forbes *et al.*, 2011), and mutated genes may be concentrated in a small number of signaling pathways. These core pathways are essential for therapeutics and/or drug design in order to examine the target protein. In addition to the analysis of single genes, the combinatorial patterns of somatic mutations were studied through large-scale sequencing data (Yeang *et al.*, 2008). The observations confirmed that the mutation signatures are heterogeneous in different tumor tissues. These patterns revealed the functional relations of genes in core pathways of cancer including cell cycle control, stress response,

Table 1: The main recent high-throughput cancer genomic studies and initiatives. (The first fourteen rows are from Baudot *et al.*, 2009, Table 1)

Study	**Gene**	**Tumor**	**Screen size**	**PM ID**
Bardelli *et al.*, 2003	Tyrosine kinase	Colon	138 genes, 35 samples, a subset in 147 additional samples	12738854
Wang *et al.*, 2004	Tyrosine phosphatase	Colon	87 genes, 18 samples, a subset in 157 additional samples	15155950
Stephens *et al.*, 2005	Kinase	Breast	518 genes, 25 samples, a subset in 56 additional samples	15908952
Davies *et al.*, 2005	Kinase	Lung	518 genes, 33 samples, a subset in 56 additional samples	16140923
Sjöblom *et al.*, 2006	All	Breast & colon	13,023 genes, 22 samples, a subset in 48 additional samples	16959974
Greenman *et al.*, 2007	Kinase	210 human cancers	518 genes in 210 samples	17344846
Wood *et al.*, 2007	All	Breast and colon	18,191 genes, 22 samples, a subset in 48 additional samples	17932254
Loriaux *et al.*, 2008	Tyrosine kinase	Acute myeloid leukaemia	85 genes, 188 samples	18252861
Tomasson *et al.*, 2008	Tyrosine kinase	Acute myeloid leukaemia	26 genes, 94 samples, a subset in 94 additional samples	18270328
Brown *et al.*, 2008	Tyrosine kinase	Chronic lymphocytic leukaemia	70 genes, 95 samples	18754031
Jones *et al.*, 2008	All	Pancreas	20,661 genes, 24 samples	18772397
Parsons *et al.*, 2008	All	Glioblastoma	20,661 genes, 22 samples, a subset in 83 additional samples	18772396
TCGA, 2008	601 genes	Glioblastoma	601 genes, 91 samples	18772890
Ding *et al.*, 2008	623 genes	Lung	623 genes, 188 samples	18948947
Yeang *et al.*, 2008	All	210 human cancers	3303 genes, 45 cancer tissues, 218323 cancer samples and 514020 records from 4138 studies	18434431
Bignell *et al.*, 2010	All	Cancer cell lines	746 cancer cell lines with 2428 somatic homozygous deletions	20164919

IGF-AKT, TGF-β, WNT and RAS pathways. Their subsumption relations revealed the order of mutational events. Furthermore, the observed mutational patterns suggested new co-sequencing targets that could be applied to reveal novel patterns and/or validate the predictions from the existing patterns. These analyses are based on previous knowledge of known pathways and gene functions and provide insights into the tumorigenesis.

So far, at least 390 (1.7%) of about 22,000 protein-coding genes have been reported as drivers with strong evidence (Stratton *et al.*, 2009) (http://www.sanger.ac.uk/genetics/CGP/Census/). About 90% are somatic mutations, whereas about 20% and 10% are germline mutations and both germline and somatic mutations, respectively. Most of them were discovered by their physical locations in the genome, while a few drivers were guided by functional analysis and feasible information from the previous studies (Stratton *et al.*, 2009). The low-resolution

genome-wide screens and in particular cytogenetics for chromosomal translocations (Drexler *et al.*, 1995) are the main tools to explore the locations of genetic aberrations. The cancer genes in germlines were identified by genetic linkage analysis (Antoniou and Easton, 2006) (see for example, Palmieri *et al.*, 2002; te Velde and Pearson, 2002; Kok *et al.*, 2005).

The functional characteristics of drivers were classified as gain- or loss-of-function mutations (Weinberg, 2007). Oncogenes are involved in cell growth and differentiation. By definition, these genes possess gain-of-function mutations or dominant effects in cancer (Stratton *et al.*, 2009). Conversely, tumor suppressor genes are anti-oncogenes that inhibit cellular proliferation. These genes possess loss-of-function mutations or recessive effects in cancer. Most known somatically mutated cancer genes are dominant: alterations on one allele suffice to activate/enhance the function of the protein and facilitate oncogenesis. In contrast, aberrations on both alleles of recessive genes are required to provoke proliferation by abolishing the protein function. The genes that participate in these pathways and their cascade mechanisms are summarized in Table 2.

3. Databases of Somatic Mutations and Integrative Analyses in Cancer Genomic Data

The Catalog of Somatic Mutations in Cancer (COSMIC) (http://www.sanger.ac.uk/perl/genetics/CGP/cosmic) is the largest public resource for information on somatic mutations in cancer (Forbes *et al.*, 2010). Mutational records (primarily point mutations and small-scale insertions/deletions) of human cancers are extracted from a large number of prior publications. COSMIC data is primarily web-driven, focused on providing mutation range and frequency statistics based upon a choice of gene and/or cancer phenotype. Based on v. 51 (January, 2011), COSMIC encompasses 19,001 genes screened from 580,306 samples in 2.9 million experiments and reports 167,193 mutations (Table 3). In addition to COSMIC, Wellcome Trust Sanger Institute also provides other related projects including Cancer Gene Census (CGC) (http://www.sanger.ac.uk/genetics/CGP/Census/), Genome Wide LOH and Copy Number Analysis (http://www.sanger.ac.uk/genetics/CGP/CopyNumberMapping/), NCI-60 Cancer Cell Line Mutation Data (http://www.sanger.ac.uk/genetics/CGP/NCI60/), Cancer Cell Line Project (http://www.sanger.ac.uk/genetics/CGP/CellLines/), Genomics of Drug Sensitivity in Cancer (http://www.sanger.ac.uk/genetics/CGP/translation/). Although these projects focus on different aspects of gene mutations (see Table 4), the ultimate goal is the same: to provide comprehensive and feasible sources of human cancer genomes. In the past few years, the cancer genome sequencing studies have been substantially growing in size, in which most of candidate genes were cataloged in COSMIC.

Table 2: Summary of human oncogenes and tumor suppressor genes. (Adopted from Weinberg, 2007 and data collected from Cancer Gene Census database (version 15 November 2011)

Pathway	Gene	GenesID	ChrBand	Type*	Alteration	Capability	Tumor Types		Tissue Type	Translocation Partner
							Somatic Mutations	Germline mutations		
Cell cycle	*Abl*	25	9q34.1	O	T, Mis	Γ	CML, T-ALL, ALL	-	L	BCR, ETV6, NUP214
	Cdk2	1017	12q13	O	A, I, D, Mis, N, F, S	Γ	Rb, Breast, Prostate, Colorectal, Pancreas, multiple tumors	-	L, E, M	-
	Cdk4	1019	12q14	O	P, Mis	Γ	-	MLN	E	-
	Cyclin D	595	11q13	O	A, T	Γ	CLL, B-ALL, Breast, Bladder	-	L, E	IGH@, STL3
	Cyclin E	898	19q12	O	A	Γ	Rb, MDB, Breast, Serous, Ovarian, Bladder, Liver	-	E	-
	p15	1030	9p21	S	P	Γ	Rb, T-ALL, ALL, Lung, Breast, multiple tumors	-	L, E, M	-

Table 2 (continued): Summary of human oncogenes and tumor suppressor genes. (Adopted from Weinberg, 2007 and data collected from Cancer Gene Census database (version 15 November 2011)

Pathway	Gene	GenesID	ChrBand	Type*	Alteration	Capability	Tumor Types		Tissue Type	Translocation Partner
							Somatic Mutations	Germline mutations		
Cell cycle	*p16*	1029	9p21	S	P, D, Mis, N, F, S	Γ	MLN, multiple tumor types	MLN, Pancreas	L, E, M	-
	p21	1026	6p21.2	S	P	Γ	Rb, Colorectal, Breast, Prostate	MLN, Breast	L, E, M	-
	Rb	5925	13q14	S	P, D, Mis, N, F, S	Γ	Rb, Sarcoma, Breast, SCLC	Rb, Sarcoma, Breast, SCLC	L, E, M	-
	EGFR	1956	7p12.3-p12.1	O	A, Mis	Γ	Glioma, NSCLC	NSCLC	E	-
DNA damage	*Aurora A*	6790	20q13	O	A, I	Γ	Breast, ALL, Colorectal, Gastric, Glioma, Ovarian, Lung, Rental, Bladder, MDB	-	L, E, M	-
	HPV-E6	1489078	HpV16 gp	O	V	†	Cervical, Breast, Head and neck squamous cell carcinoma	-	E	-

Table 2 (continued): Summary of human oncogenes and tumor suppressor genes. (Adopted from Weinberg, 2007 and data collected from Cancer Gene Census database (version 15 November 2011)

Pathway	Gene	GenesID	ChrBand	Type*	Alteration	Capability	Tumor Types		Tissue Type	Translocation Partner
							Somatic Mutations	Germline mutations		
DNA damage	*MDM2*	4193	12q15	O	A	†	Sarcoma, Glioma, Colorectal	-	L, E, M	-
	ARF	1029	9p21	S	P, D, S	Γ	MLN, multiple other tumor types	MLN, Pancreas	L, E, M	-
	ATM/ATR	472	11q22.3	S	P, D, Mis, N, F, S	∅	T-PLL	Leukemia, Glioma, lLymphoma, MDB	L	-
	BRCA1	672	17q21	S	P, D, Mis, N, F, S	Γ, ∅	Ovarian	Breast, Ovarian	E	-
	Chk1	1111	11q24.2	S	P	∅	Colorectal, MLL, Rb, Lymphoid neoplasm	-	L, E, M	-
	Chk2	11200	22q12.1	S	P, F	∅	-	Breast	E	-

Table 2 (continued): Summary of human oncogenes and tumor suppressor genes. (Adopted from Weinberg, 2007 and data collected from Cancer Gene Census database (version 15 November 2011)

Pathway	Gene	GenesID	ChrBand	Type*	Alteration	Capability	Tumor Types		Tissue Type	Translocation Partner
							Somatic Mutations	Germline mutations		
DNA damage	*DNA-PK*	5591	8q11	S	P, F	∅	LA, MLN, Colorectal, LSCC, Glioma	-	E	-
	FANCD2	2177	3p26	S	P	∅	-	AML	L	-
	HIPK2	28996	7q32-q34	S	P	†, Γ	-	AML	L	-
	NBS1	4683	8q21	S	P, D, Mis, N, F	∅	-	NHL, Glioma, MDB, RMS	L, E, M	-
							Breast, Colorectal, Lung, Sarcoma, Adrenocortical, Glioma	Breast, Sarcoma, Adrenocortical, Carcinoma, Glioma, multiple other tumor types	L, E, M	-
TGFβ	*Myc*	4609	8q24.12-q24.13	O	P, A, T	Γ	Burkitt lymphoma, amplified in other cancers, B-CLL	-	L, E	IGK@, CL5, BCL7A, TG1, TRA@, GH@
	BMPR	657	10q22.3	S	P, Mis, N, F	∅	-	GIP	E	-
	Smad2/3	4087/ 4088	18q21.1/ 15q22.33	S	P	∅	Colorectal	-	E	-
	Smad4	4089	18q21.1	S	P	∅	-	Colorectal	E	-
	TGFβ R	7048	3p22	S	P, Mis, F	∅	Colorectal, LNDC, Esophageal	-	E	-

Table 2 (continued): Summary of human oncogenes and tumor suppressor genes. (Adopted from Weinberg, 2007 and data collected from Cancer Gene Census database (version 15 November 2011)

Pathway	Gene	GenesID	ChrBand	Type*	Alteration	Capability	Tumor Types		Tissue Type	Translocation Partner
							Somatic Mutations	Germline mutations		
Wnt	*β-catenin*	1499	3p22-p21.3	O	P, H, Mis, T	Γ	Colorectal, Ovarian, Hepatoblastoma, Pleomorphic	-	E, M	PLAG1
	RAR	5914	17q12	O	A, T	Γ	APL	-	L	PML, NF145, TIF1, UMA1, NPM1
	SOX	6657	3q26.3-q27	O	A, I	Γ	NSCLC, OSCC	-	E	-
	Wnt1	7471	12q13	O	I	Γ	Breast, Colorectal, HCC	-	E, M	-
	APC	324	5q21	S	P, D, Mis, N, F, S	Γ	Colorectal, Pancreas, Desmoid, HBC, Glioma, other CNS	Colorectal, Pancreas, Desmoid, HBCs, Glioma, other CNS	E, M	-
	Axin	8312, 7313	16p13.3, 17q23-q24	S	P, D, Mis, N	Γ	HCC, HBC, Colorectal, Ovarian, MB	Colorectal	E, M	-
	α-catenin	1495	5q31.2	S	P, D, Mis, N, I,	III	Lung, Prostate, Ovarian, Colorectal	-	E, M	-
	E-cadherin	999	16q22.1	S	P, Mis, N, F, S	Γ, ∅, III	Breast, Gastric	Gastric	E	-

Table 2 (continued): Summary of human oncogenes and tumor suppressor genes. (Adopted from Weinberg, 2007 and data collected from Cancer Gene Census database (version 15 November 2011)

Pathway	Gene	GenesID	ChrBand	Type*	Alteration	Capability	Tumor Types		Tissue Type	Translocation Partner
							Somatic Mutations	Germline mutations		
Wnt	*Wnt5A*	7474	3p21-p14	S	P	Γ	Breast, Gastric, Colorectal, MLN, Thyroid, Prostate, Ovarian, Lung	-	L, E	-
GPCR	*GPCRs*	20 alpha, 6 beta, 11 gamma subunits (Schlessinger, 2000)		O	P	Γ	SCLC, HNSCC, Pancreas, Ovarian, Prostate, multiple tumors	-	E	-
Ras	*B-Raf*	673	7q34	O	P, Mis, T	Γ	MLN, Colorectal, Papillary thyroid, Borderline, NSCLC, Cholangiocarcinoma, Pilocytic astrocytoma	-	E	AKAP9, KIAA1549
	Fos/Jun	2353, 3725	14q24.3, 1p32-p31	O	A, I	†, Γ	Sarcoma	-	M	-
	ILK	3611	1p15.4	O	I, Mis	Γ, Ш	Ovarian, Prostate, MLN, multiple tumors	-	L, E, M	-
	Ras	3845	12p12.1	O	P, Mis	Γ	Pancreas, Colorectal, Lung, Thyroid, AML	-	L, E, M	-

Table 2 (continued): Summary of human oncogenes and tumor suppressor genes. (Adopted from Weinberg, 2007 and data collected from Cancer Gene Census database (version 15 November 2011)

Pathway	Gene	GenesID	ChrBand	Type*	Alteration	Capability	Tumor Types		Tissue Type	Translocation Partner
							Somatic Mutations	Germline mutations		
Ras	*RTKs*	20 families of receptor tyrosine kinases (Matise and Joyner, 1999)		O	P, T, A, I	†, Γ, Ш, Θ	Breast, Ovarian, Gastric, Lung, Bladder, multi tumors	Rental	L, E, M	PDGF, DK1, PKB, PLC_{γ}
	Integrin	18 alpha, 8 beta subunits (Merlo *et al.*, 2006)		S	D	Ш	Breast, MLN, Pancreas, Renal, Colorectal, Ovarian, Glioblastoma, Lung	Ovarian	E	-
	NF1	4763	17q12	S	P, D, Mis, N, F, S,	Γ	Neurofibroma, Glioma	Neurofibroma, Glioma	E	-
	VHL	7428	3p25	S	P, D, Mis, N, F, S	Θ	Renal, Hemangioma, Pheochromocytoma	Renal, Hemangioma, Pheochromocytoma	E, M	-
Akt	*Akt*	207, 208	14q32.3, 19q13.1-q13.2	O	P, A, I, Mis	†	Breast, colorectal, ovarian, NSCLC, Pancreas	-	E	-
	Bax	581	19q13.3-q13.4	O	P	†	Breast, Colorectal, Prostate, Gastric, ALL	-	L, E	-

Table 2 (continued): Summary of human oncogenes and tumor suppressor genes. (Adopted from Weinberg, 2007 and data collected from Cancer Gene Census database (version 15 November 2011)

Pathway	Gene	GenesID	ChrBand	Type*	Alteration	Capability	Tumor Types		Tissue Type	Translocation Partner
							Somatic Mutations	Germline mutations		
Akt	*TSC1, TSC2*	7248, 7279	9q34, 16p13.3	S	P, D, Mis, N, F, S	Γ	-	Hematoma, Renal	E	-
	Akt	207, 208	14q32.3, 19q13.1-q13.2	O	P, A, I, Mis	†	Breast, colorectal, ovarian, NSCLC, Pancreas	-	E	-
	Bax	581	19q13.3-q13.4	O	P	†	Breast, Colorectal, Prostate, Gastric, ALL	-	L, E	-
	FKHR/ FOXO	2308	13q14.1	O	T	†	ARM	-	M	PAX3
	JAK	3716, 3717, 3718	1p32.3-p31.3, 9p24, 19p13.1	O	P, T, Mis	†, Γ	ALL, AML, MPD, CML	-	L	ETV6, PCM1, BCR
	PI3K	5290	3q26.3	O	P, Mis	†	Colorectal, Gastric, Gliobastoma, Breast	-	E	-
	Bcl-2	596	18q21.3	S	T	†	NHL, CLL	-	L	IGH@
	LKB1	6794	19p13.3	S	P, D, Mis, N, F, S	Γ	NSCLC, Pancreas	JHH, Ovarian, Testicular, Pancreas	E, M	-
	PTEN	5728	10q23.3	S	P, D, Mis, N, F, S	†	Glioma, Prostate, Endometrial	Hematoma, Glioma, Prostate, Endometrial	L, E, M	-
	TSC1, TSC2	7248, 7279	9q34, 16p13.3	S	P, D, Mis, N, F, S	Γ	-	Hematoma, Renal	E	-
Death Receptor	*Fas*	355	10q24.1	O	P, Mis	†	TGCT, nasal NK/T lymphoma, SCC	-	L, E	-

Table 2 (continued): Summary of human oncogenes and tumor suppressor genes. (Adopted from Weinberg, 2007 and data collected from Cancer Gene Census database (version 15 November 2011)

Pathway	Gene	GenesID	ChrBand	Type*	Alteration	Capability	Tumor Types		Tissue Type	Translocation Partner
							Somatic Mutations	Germline mutations		
Notch	*Notch1, Notch2*	4851, 4853	9q34.3, 1p13-p11	O	T, Mis	†	T-ALL, Marginal zone lymphoma, DLBCL	-	L	TRB@
Hedgehog	*Gli family (Gli1-Gli3)*	2735, 2736, 2737	12q13.2-q13.3, 2q14, 7p13	O	A, T	†, Γ	Glioblastoma, Prostate, Breast, Colorectal	-	E	-
	Hedgehog (SHH, IHH, DHH)	6469, 3549, 50846	7q36, 2q33-q35, 12q13.1	O	P, Mis, N, F	†, Γ	Prostate, MDB, Gastric, BCC	-	E	-
	Smo	6608	7q31-q32	O	P, Mis	†, Γ	Skin basal cell	-	E	-
	Ptch	5727	9q22.3	S	P, Mis, N, F, S	†, Γ	Skin basal cell, MB	Skin basal cell, MB	E, M	-
	Su(Fu)	51684	10q24.32	S	P, D, F, S	†, Γ	MB	MB	E	-

* O = Oncogenes, S = Tumor suppressors. P = Point mutations, A = Amplification, I = Increased expression, D = Deletion, F = Frameshift, Mis = Missense, N = nonsense, S = Splice site, T = Translocation. E = Epithelial, L= Lymphoma, M = Mesenchymal. AML = Acute myelogenous leukemia, APL = acute promyelocytic leukemia, ARM = Alveolar rhabdomyosarcoma, B-ALL = B-cell acute lymphocytic leukaemia, B-CLL = B-cell lymphocytic leukemia, B-NHL = B-cell non-Hodgkin lymphoma, BCC = Basal cell carcinoma, CML = Chronic myeloid leukemia, CNS = Central nervous system, GIP = Gastrointestinal polyp, HBC = Hepatoblsastoma carcinoma, HCC = Hepatocellular carcinoma, JJH = Jejunal hematoma, LA = Lung adenocarcinoma, LNDC = Lung neuroendocrine carcinoma, MPD = Myelot-proliferative disorder, MB = Medulloblastoma, MLN = Melanoma, MLL = Murine L1210 leukemia, NK/T = Natural killer T cell, NHL = Non-Hodgkin lymphoma, NSCLC = Non small cell lung cancer, OSCC = Oesophageal squamous cell carcinoma, Rb = Retinoblastoma, SCC = Skin squamous cell Ca -burn scar-related, T-ALL = T-cell acute lymphoblastic leukemia, T-CLL = T-cell chronic lymphocytic leukaemia, T-PLL = T cell prolymphocytic leukaemia, TGCT = Testicular germ cell tumor. † = Evading apoptosis, Γ = Self-sufficiency in growth signals, ∅ = Insensitivity to anti-growth signals, Ш = Tissue invasion and metastasis, ∞ = Limitless replicative potential, Θ = Sustained angiogenesis.

Table 3: Examples of statistics in COSMIC v.51 (January, 2011), Cancer Cell Line Project (November, 2010) and Cancer Gene Census (December, 2010) (see details of genes from (Futreal *et al.*, Suppl 1, 2004))

COSMIC		**Cancer Cell Line Project**						**Gene Census**	
Variant	**Statistics**	**Gene name**	**# Mut**	**Gene name**	**# Mut**	**Gene name**	**# Mut**	**Sorted By**	**Statistics**
Experiments	2946792	*ALK*	3	*FGFR3*	2	*NOTCH1*	16	Amplification	14
Tumours	577304	*APC*	35	*FLCN*	3	*NRAS*	48	Chromosome	436
Samples	580306	*BRAF*	66	*FLT3*	4	*PIK3CA*	64	Frameshift mutation	82
Mutant	161787	*BRCA1*	2	*GNAS*	1	*PIK3R1*	13	Germline mutation	74
Samples		*BRCA2*	6	*HRAS*	8	*PTEN*	104	Large deletion	33
Mutations	167193	*CDH1*	12	*IDH1*	1	*RB1*	107	Missense mutation	118
Unique	41405	*CDKN2Aa*	293	*JAK2*	1	*RUNX1*	2	Nonsense mutation	78
Mutations		*CDKN2C*	12	*KDM5C*	4	*SETD2*	2	Other mutation	18
Papers	11062	*CDKN2a(p14)*	252	*KDM6A*	28	*SMAD4*	31	Somatic mutation	394
curated		*CTNNB1*	17	*KRAS*	89	*SMARCA4*	14	Splicing mutation	52
Genes	19001	*CYLD*	1	*MAP2K4*	16	*SOCS1*	1	Symbol	436
Fusions	5573	*EGFR*	10	*MLH1*	11	*STK11*	32	Translocation	301
Structural	2729	*ERBB2*	2	*MSH2*	11	*TET2*	3		
Variants		EZH2	5	*MSH6*	8	*TP53*	495		
		FAM123B	5	*NF1*	24	*TSC1*	4		
		FBXW7	29	*NF2*	23	*VHL*	7		

Table 4: Available data on ICGC (November, 2010), TCGA (February, 2011) and other sources. (May 2011) (The table is adopted from data portal of ICGC: http://dcc.icgc.org/pages/summary/)

Source	Cancer project	Dataset							
		Simple mutations	Copy number alterations	Structural rearrangements	Gene expression	miRNA expression	Exon junction	DNA methy -lation	Germline variations
ICGC	Breast Carcinoma (WTSI, UK)			24					
	Liver Cancer (NCC, JP)	1		1					
	Liver Cancer (RIKEN, JP)	1		1					
	Malignant Cancer (WTSI, UK)	1		1					
	Pancreatic Cancer (OICR, CA)	5	5		1	3			
	Pancreatic Cancer (QCMG, AU)	3	3	3	3	6	3		3
	Small Cell Lung Carcinoma (WTSI, UK) (Baer and Lee, 1998)	1		1					
TCGA	Acute Myeloid Leukemia								
	Breast Invasive Carcinoma							188	
	Colon Adenocarcinoma				371			186	
	Glioblastoma Multiforme (TCGA, 2008)	147			155			185	
	Kidney Renal Clear Cell Carcinoma				243			258	
	Kidney Renal Papillary Cell Carcinoma				41			419	

Table 4 (continued): Available data on ICGC (November, 2010), TCGA (February, 2011) and other sources. (May 2011) (The table is adopted from data portal of ICGC: http://dcc.icgc.org/pages/summary/)

Source	Cancer project	Dataset							
		Simple mutations	Copy number alterations	Structural rearrangements	Gene expression	miRNA expression	Exon junction	DNA methylation	Germline variations
TCGA	Lung Adenocarcinoma							22	
	Lung Squamous Cell Carcinoma				32			153	
	Ovarian Serous Cystadenocarcinoma (TCGA, 2011)	185			134			160	
	Rectum Adenocarcinoma				525			545	
	Stomach Adenocarcinoma				69			73	
	Uterine Corpus Endometrioid Carcinoma							142	
Other	Breast Cancer (JHU, US) (Wood *et al.*, 2007)	42						71	
	Colorectal Cancer (JHU, US) (Wood *et al.*, 2007; Sjöblom *et al.*, 2006)	36							
	Glioblastoma Multiforme (JHU, US) (Aerts *et al.*, 2006)	89	22						
	Lung Adenocarcinoma (TSP, US) (Ding *et al.*, 2008)	163							
	Pancreatic Cancer (JHU, US) (Jones *et al.*, 2008)	114	24						

The Cancer Genome Atlas (TCGA) (http://tcga-data.nci.nih.gov/tcga/) is another international collaborative effort led by National Institute of Health (NIH) to comprehensively catalog somatic DNA changes from the genomes of cancer specimens and associated normal tissues in at least 400 to 1,000 cancer cases (TCGA, 2008). The International Cancer Genome Consortium (ICGC) (http://www.icgc.org/) is aiming for comprehensively characterizing somatic aberrations of at least fifty classes of cancers with high-coverage sequencing of 25,000 cancer genomes or more (ICGC, 2010). The released data of TCGA and ICGC are summarized in Table 4.

Broadly speaking, cancer genomic data can be divided into four levels: (I) raw, (II) processed or normalized, (III) interpreted, and (IV) summarized categories based on the degree of computational analysis applied to the data (Chin *et al.*, 2011). Level I-III data correspond to individual samples, while level IV refers to analyses across datasets. Processed or normalized data represent the data that have been assigned to a genome reference such as alignment of sequences to reference genome or combination of multiple probes to a single value in a microarray. Interpreted data represent biological meanings extracted from each sample such as comparisons of expression profiles across the genes. Summarized data represent analysis of interpreted data across a cohort of samples. In order to protect patient privacy, access policies are applied to the data. Most raw data and some type of normalized data such as single nucleotide polymorphism profiles have controlled to limited users, while interpreted and summarized data are openly accessible to all users. Controlled-access data typically require a specific proposal of data use and approval by the institutional board of the requesting investigator. Sites of these databases including data structures and access policies are summarized in Chin *et al.* (2011), Table 2 and provided on the public website http://mib.stat.sinica.edu.tw/yeanggroup/public/cancerdb.

Up to date, challenges in analysis of cancer genome data are subjected to four aspects: (1) quality control (QC) of data, (2) accurate estimation of signal and noise in large data sets, (3) reproducible approaches to complex genomic analyses, and (4) achieving sufficient power in the face of multiple hypotheses testing (Chin *et al.*, 2011). Biospecimen and technical execution are key factors contributing to raw data quality. Criteria in normalization step are important to remove any experimental artifacts that may negatively impact data quality. Platform-specific noise measures can be used to optimize data quality for each type of genomic measurement. Statistical and computational approaches are powerful tools to explore such large-scale genomic studies. There are various theoretical models predicting the functional consequence of specific nucleotide mutations. Beyond statistical analysis, these models are often constructed based on the functional impacts of specific amino acid mutations on protein structures or conserved domains either in two- or three-dimension. Statistical power is a principal concern for identify-

ing biomarkers to distinguish between various phenotypes such as cancer versus normal samples. Since the feature size in these problems is typically far more than the sample size, adjustment of inference outcomes in multiple hypotheses testing such as Bonferroni correction (Abdi, 2007) or false discovery rates (FDR) (Benjamini and Hochberg, 1995) needs to be applied. However, the Bonferroni correction is too conservative for relevant variables (Perneger, 1998). Another challenge to validate the alteration patterns in cancer is the reproducibility of the findings in independent data sets. Computational tools such as meta-analysis across multiple datasets can facilitate validation of reproducible findings (Hong *et al.*, 2006).

Cancer cells undergo alterations at multiple levels from DNA sequences and karyotypes to RNA expressions and protein modifications. Integrative analysis is a promising tool to reveal the multi-level information of cancer cells by combining the data from multiple types of assays. There are a number of efforts on data-integration in cancer genomics. For instance, predicting candidate tumor suppressor genes from genomic deletions, inactivating mutations, promoter hypermethylation, alterations of miRNA expression and/or transcriptional downregulation in different tumor samples (Dalgliesh *et al.*, 2010), assessing pathway activities from sequence mutations and copy number variations of the member genes (TCGA, 2008), characterizing glioblastoma phenotypes with combinations of copy number variations and transcription profiles (Verhaak *et al.*, 2010), and identifying key somatic driver mutations of small-cell lung cancer based integrative analyses (Peifer *et al.*, 2012). In addition to the aforementioned studies, there are a number of books introducing broader principles and applications of computational methodologies in cancer studies. For instance, a textbook edited by Barillot *et al.* (2012) provides a comprehensive overview of the concepts and algorithms, principles of existing models/tools and relevant resources including real examples of biological applications, clinical aspects and biological questions in computational systems biology of cancer. A lecture note on mathematical modeling written by Wodarz and Komarova (2008) introduces the concept of mathematical modeling and a variety of applications in cancer biology such as somatic evolution of cells, genetic instability, and angiogenesis. The book also discusses the use of mathematical models for the analysis of therapeutic approaches such as chemotherapy, immunotherapy, and the use of oncolytic viruses. Juan (2011) published a textbook presenting an overview of the ongoing advances of genomics and proteomics in systems biology, coupled with the development of new and more robust tools in cancer-related research. As for statistical methods, the book series published by IARC (1980, 1986, 1987, 1994) cover principal issues in cancer research. The first volume (IARC, 1980) explains the statistical methods and theory behind the design, and the practical application to specific sets of data. It includes chapters on fundamental measures of disease occur-

rence, general considerations for the analysis of case-control studies, analysis of grouped and ungrouped data, and use of unconditional and conditional logistic regressions. The second volume (IARC, 1986) provides a comprehensive account of the major types of studies in cancer epidemiology. Its scope ranges from an account of elementary and descriptive cohort analyses to the fitting of regression models for incidence rates with general risk functions. Particular attention is given to the use of a case-control approach embedded in a cohort study. As in the first volume, all methods are illustrated by examples from real studies, and the data are appended to the text, enabling readers to rework the computations. The third volume (IARC, 1987) addresses the design and analysis of measures to standardize methods for long-term animal experiments. This area of research is particularly important due to the biological limitations of short-term assays and the methodological difficulties of some epidemiological studies. The fourth volume (IARC, 1994) presents and discusses fundamental concepts, techniques for the analysis of cancer risk, space-time variations and group correlations and technique for survival analysis, that used in descriptive epidemiology which are relevant to cancer research.

4. Common and Different Causes among Distinct Cancer Types

Carcinogenesis is a multistep process requiring the accumulation of multiple genetic mutations. The common features of tumor cells include immortality, decreased dependence on growth factors to support proliferation, loss of anchorage-dependent growth, loss of cell cycle control, reduced sensitivity to apoptotic cell death, and increased genetic instability. The mutations of genes that dysregulate the activities of these molecular features can consequently increase a risk of tumorigenesis. However, the development of cancer phenotypes among different tissues differs on selective constraints and trajectories of evolution (Merlo *et al.*, 2006). Identification of the molecular aberrations characterizing the phenotypes of cancers is of great importance in their diagnosis and treatments. During 2004 to 2008, World Health Organization (WHO) has investigated cancer statistics in distinct cancer types via a project named GLOBOCAN (http://globocan.iarc.fr/). The aim of the project is to provide contemporary estimates of the incidence, mortality and prevalence from major type of cancers, at national level, for 184 countries of the world. The latest GLOBOCAN estimates are presented in 2008 (Ferlay *et al.*, 2008). This review summarizes the common and distinct genetic mutations in five distinct cancer types possessing the highest incidence and mortality worldwide (lung, breast, colorectum, stomach and prostate), and another one cancer type (brain with glioblastoma multiforme) as the first effort of integrative analysis in cancer genomic data (TCGA, 2008). The cancer statistics and method summary in GLOBOCAN are shown in Table 5. The mutated genes and

related pathways of several common cancer types are summarized in Table 2.

Table 5: Method and statistics summary of estimating age-standardized incidence, mortality and prevalence in male, female and both sexes (GLOBOCAN, 2008). Incidence: Population weighted average of the area-specific country rates applied to the 2008 area population. Mortality: Population weighted average of the area-specific country rates applied to the 2008 area population. Prevalence: Sum of area-specific prevalent cases. Age-standardised rate (W): A rate is the number of new cases or deaths per 100,000 persons per year. Risk of getting or dying from the disease before age 75 (%): The probability or risk of individuals getting/dying from cancer

World	**Male**	**Female**	**Both sexes**
Population (thousands)	3414566	3358715	6773281
Number of new cancer cases (thousands)	6617.8	6044.7	12662.6
Age-standardized rate (W)	202.8	164.4	180.8
Risk of getting cancer before age 75 (%)	21.1	16.5	18.6
Number of cancer deaths (thousands)	4219.6	3345.2	7564.8
Age-standardized rate (W)	127.9	87.2	105.6
Risk of dying from cancer before age 75 (%)	13.4	9.1	11.1
5-year prevalent cases, adult population (thousands)	13514.9	15288.3	28803.2
Proportion (per 100,000)	550.6	620.8	585.8
5 most frequent cancers	Lung	Breast	**Lung**
(ranking defined by total number of cases)	Prostate	Colorectum	**Breast**
	Colorectum	Cervix uteri	**Colorectum**
	Stomach	Lung	**Stomach**
	Liver	Stomach	**Prostate**

Lung cancer is the leading cause of cancer mortality in both men and women in the United States (Travis *et al.*, 1995) and has the highest incidence rate (age-standardized) of all cancers in the North America, Eastern Asia and Europe for males, and in the North America, Northern Europe, Eastern Asia, Australia and New Zealand for females (McDonald *et al.*, 2008; Ferlay *et al.*, 2008). Polymorphisms in interleukin-1 (Engels *et al.*, 2007; Lind *et al.*, 2005), cytochrome P450 (Wenzlaff *et al.*, 2005), caspase-9 (Park *et al.*, 2002), and nucleotide excision repair molecules (Park *et al.*, 2006) render higher risks for lung cancer after exposure to carcinogens or mutagens. Genetic alterations in smokers and nonsmokers with lung cancers have different molecular profiles. Mutations and amplifications of the epidermal growth factor *EGFR* kinase domain commonly occur in the early development of adenocarcinoma, which is generally unrelated to smoking (Herbst and Schwartz, 2008). Mutations in the *K-RAS* proto-oncogene occur more frequently among smoker patients and comprise 10-30% of lung adenocarcinomas (Jančík *et al.*, 2010). *HER2* mutations and amplifications have been identified in patients with lung adenocarcnima (Stephens *et al.*, 2004; Shigematsu *et al.*,

2005; Buttitta *et al.*, 2006). Kinase domain mutations of *HER2* and *EGFR* are associated with non-smoking Asian women with lung cancers (Shigematsu *et al.*, 2005). Meanwhile, amplifications of *HER2* are associated with sensitivity to inhibitors of *EGFR* tyrosine kinase (Herbst and Schwartz, 2008). Loss of heterozygosity can inactivate several tumor suppressors such as *p53* (Zienolddiny *et al.*, 2001), *c-MET* (Ma *et al.*, 2005), *LKB1* (Sanchez-Cespedes *et al.*, 2002), *PIK3CA* (Samuels and Velculescu, 2004), and *BRAF* (Brose *et al.*, 2002). The mutations in these genes affect several major downstream signaling pathways including Ras-Raf-Mek and the pathway consisting of phosphoinositide 3-kinase (PI3K), Akt, and mammalian target of rapamycin (mTOR), which may participate in proliferation, invasion, metastasis, and tumor angiogenesis through pathways of hypoxia inducible factor (HIF) (Volm and Koomägi, 2000). These pathways may be modulated by other receptor tyrosine kinases, such as insulin-like growth factor 1 receptor (IGF-1R) and *c-MET*, and by the LKB1-amp-activated protein kinase (AMPK) pathway (Herbst and Schwartz, 2008). Furthermore, other alterations such as methylation in promoter regions and microsatellite instability can occur in normal tissue surrounding non-small-cell lung tumors and may be associated with a risk of recurrence and second primary tumors (Park *et al.*, 2000). In summary, these studies suggest that molecular origins and mechanisms of lung cancer are complex interactions between environment and genes.

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths in women in both developed and developing countries (Jemal *et al.*, 2011). A number of genes conferring risks of breast cancers have been identified, including *BRCA1*, *BRCA2*, *ATM*, *TP53*, *CHEK2*, *PTEN*, *CDH1* and *SKT11*. Mutations on these genes can be either inherited or acquired (Ergül and Sazc, 2001). The inherited mutations of *BRCA1* and *BRCA2* are the most common cause of hereditary breast cancer. Women carrying *BRCA1* or *BRCA2* mutations possess a risk 80% higher than women without inherited mutations. *ATM* is involved in DNA damage repeat. Mutations on one or two copies of this gene yield a high rate of breast cancer and the disease ataxia-telangiectasia. Inherited mutations of *p53* and *CHECK2* cause the Li-Fraumeni syndrome and elevate the risk of breast cancer (Vickie and Saundra, 2010). Inherited mutations in *PTEN* lead to Cowden syndrome, a rare disorder that increases risk for both benign and malignant breast cancer (Lynch *et al.*, 1997). Inherited mutations in *CDH1* indirectly increase risk of invasive lobular breast cancer via a hereditary diffuse gastric cancer (Graziano *et al.*, 2003). The defects in *STK11* can lead to Peutz-Jeghers syndrome, a disorder in which people have pigmented spots on their lips, mouths, polyps in urinary and gastrointestinal tracts, and suffer an increasing risk of breast cancer (Hearle *et al.*, 2006). Most of these mutations are related to several signaling cascades involved in growth factor receptors and apoptosis (Lynch *et al.*, 1997). High PI3K/PTEN/Akt activities inhibit apoptosis and

activate all cycle progression, whereas high Raf activities induce growth arrest and differentiation (Steelman *et al.*, 2011). Amplification of *HER2*, a receptor tyrosine kinase (*RTK*), occurs in approximately 30% of breast cancer and lead to increased expression of both the Ras/PI3K/Akt/PTEN/mTOR and Ras/Raf/MEK/ERK pathways. In addition, many studies have examined that women with higher levels of estrogen tend to develop breast cancer (Thomas *et al.*, 1997). Estrogen can indirectly stimulate cell division by activating a variety of hormone receptors. The mechanisms of how estrogens contribute to each phase of the carcinogenesis are still unclear. Two pathways are suspected to play important role in cell proliferation and apoptosis in mammary tissues: genotoxic estrogen metabolism and estrogen-receptor-mediated genomic and nongenomic signaling (Thomas *et al.*, 1997; Clemons and Goss, 2001; Yager *et al.*, 2006). However, the factors driving these pathways require further investigation (Yager *et al.*, 2006).

Colorectal cancer is the third most commonly diagnosed cancer worldwide and more common in developed countries (Jemal *et al.*, 2011). Mutations in the Wnt-APC-beta-catenin signaling increase the signaling activity in the intestinal crypt stem cells (Segditsas and Tomlinson, 2006). The most commonly mutated gene in all colorectal cancer is *APC*. The *APC* protein interrupts stem cell renewal and differentiation by inducing high level of β-catenin protein accumulation. Mutations of *TP53* can transform an adenoma into an invasive carcinoma (Iacopetta, 2003). Other apoptotic proteins commonly deactivated in colorectal cancers are TGF-β and DCC (Markowitz, 2009). In addition, some common oncogenes such as KRAS, RAF and PI3K are overexpressed in colorectal cancers (De Roock *et al.*, 2010).

Stomach cancer, also-called gastric cancer, is one of the leading causes of cancer mortality worldwide with more than 700,000 deaths each year (Ferlay *et al.*, 2008). Stomach cancer is more common in men and most people diagnosed are over 70 years old. Stomach cancer usually begins in cells in the inner layer of the stomach. Over time, the cancer may invade more deeply into the stomach wall, and spread to surrounding organs such as liver, pancreas, esophagus, or intestine. In term of genetic alterations, gastric carcinoma organizes different patterns of interplay between neoplastic and stromal cells through the growth factor/cytokine receptor system, which has a critical role in cell growth, apoptosis, morphogenesis, angiogenesis and metastasis. Other genetic factors, such as genetic instability and DNA polymorphism are associated with increased risk levels. Two interdependent phenotypes of genomic instability are generally recognized in gastric cancer: microsatellite instability (MSI) and chromosomal instability (CIN). MSI is a common feature of gastric cancer pertaining to the DNA mismatch repair system and the DNA replication errors in simple repetitive sequences (Imai and Yamamoto, 2008). Functional inactivation by mutations or epigenetic mecha-

nisms of mismatch repair genes such as *hMLH1* and *hMSH2* has been discovered (Simpson *et al.*, 2001). MSI-related mutations occur in genes regulating cell-cycle and apoptotic signaling including *TGFβRII*, *IGFIIR*, *TCF4*, *RIZ*, *BAX*, *CASPASE5*, *FAS*, *BCL10* and *APAF1* (Lacopetta *et al.*, 1999). In addition, genes involved in genomic integrity maintenance such as *hMSH6*, *hMSH3*, *MED1*, *RAD50*, *BLM*, *ATR* and *MRE11*, are also frequently altered (Ottini, 2004). CIN is a common feature associated with chromosomal aberrations corresponding to major modifications of DNA content. For example, changes in chromosome copy number, high level LOH, gene deletions and/or amplifications (Sugai *et al.*, 2005; Sánchez-Pérez *et al.*, 2009). All these alterations may lead to oncogene activation and/or tumor suppressor gene inactivation. The methylation of CpG islands and tumor related genes such as *APC*, *CDH1*, *DKK3*, *PTEN*, *MGMT*, *MHL1*, *CDKN2A*, *CDKN2B* and *RUNX3* have been widely reported in gastric cancer. Genetic and genomic variations occurring in genes and molecules that participate in proliferation, invasion and metastasis (e.g., growth factors and their receptors, signal transducers, cell-cycle and apoptosis regulators, cell adhesion molecules, DNA repair genes and matrix metalloproteinases) may influence the prognosis of patients with gastric cancer. The genes under these pathways such as *p53*, *p21*, *p27*, *BCL2*, *BAX*, *pRb*, *c-myc*, *Clyclin E*, *E-cadherin*, *MUC1* and *PRL-3* have been investigated (Nobili *et al.*, 2011).

Prostate cancer is the third most common cause of cancer mortality in males of all ages, worldwide (Guo and Wang, 2009). The highest incidence rates are in the developed countries of Oceania, Europe, and North America, whereas the mortality rates rise more rapidly in Asian countries (Hsing *et al.*, 2000; Jemal *et al.*, 2011). RUNX2 is a transcription factor that prevents cancer cells from undergoing apoptosis (Leav *et al.*, 2010). The PI3k/Akt signaling cascade cooperates with the transforming growth factor beta/SMAD signaling cascade to facilitate prostate cancer cell survival and protection against apoptosis (Guo and Wang, 2009). X-linked inhibitor of apoptosis (XIAP) is an inhibitor of apoptosis cascade (Straszewski-Chavez *et al.*, 2004). Macrophage inhibitory cytokine-1 (MIC-1) stimulates the focal adhesion kinase (FAK) signaling pathway, which facilitates prostate cancer proliferation (Senapati *et al.*, 2010). In addition, the androgen receptor is intensively examined for its function on cell proliferation (Zou *et al.*, 2009).

Brain tumors in recent years have replaced leukemia as the leading cause of cancer-related mortality in children (Lag *et al.*, 2011). Glioblastoma Multiforme (GBM) is the most common malignant brain tumor in adults (Travis *et al.*, 1995; TCGA, 2008; Verhaak *et al.*, 2010). Glioblastoma pathogenesis is associated with deregulation of three pathways: the RTK/RAS/PI3K pathway, the CDK/cyclin/CDK inhibitor/RB pathway, and the *p53* pathway (Verhaak *et al.*,

2010; Klinz *et al.*, 2011). In the RTK/PI3K pathway, *PTEN* is frequently deleted and mutated. Amplifications or point mutations in *EGFR*, *ERBB2*, *PDGFRA* and *MET* are suggested to co-activate the RTKs mechanism. Inactivation of the *p53* pathway can occur when homozygous deletions of the CDKN2A locus encoding both $p16^{INK4A}$ and *ARF*, and amplifications of *MDM2* and *MDM4* occur. Inactivation of *RB1* by nucleotide substitutions can prevent the genetic pressure for activation of upstream cyclin/cyclin-dependent kinases. Subtypes of GBM tend to posses different mutational signatures. In classical subtypes, *EGFR* amplifications and *PTEN* mutations occur more frequently, where as *TP53* and *PDGFRA*/*IDH1*, and *NF1* mutations occur more commonly in proneural and mesenchymal subtypes (Klinz *et al.*, 2011). However, none of these alterations can distinguish subtypes of GBMs with high accuracy.

5. Conclusion

With high-throughput technologies such as SNP arrays and next-generation sequencing, the genome-wide landscape of sequence mutations is being mapped. This mutational landscape suggests that sequence mutations result from an evolution-like process. While a few cancer-related genes exhibit frequent, tissue-specific mutations and specific combinatorial mutational patterns, a large number of passenger mutations are sporadic and do not carry obvious functional consequences. However, the mutations of these well-known genes are certainly not sufficient conditions for tumorigenesis. Other types of molecular aberrations (such as epigenetic changes), biological processes beyond standard cell cycle control and apoptosis pathways (such as compromise of immune systems), small but significant effects from common variations, and interactions with environmental factors all play important roles in tumor generation. It remains a grand challenge to collect these types of information and use them to decipher the molecular mechanisms of cancer. Moreover, integrative analysis of the collected multi-modal data is a critical step toward a comprehensive understanding of oncogenesis.

Acknowledgements

This study is financially supported by the Institute of Statistical Science, Academia Sinica, Taiwan.

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Received May 29, 2012; accepted March 21, 2013.

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