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Mutations of Chromatin Structure Regulating Genes in Human Malignancies

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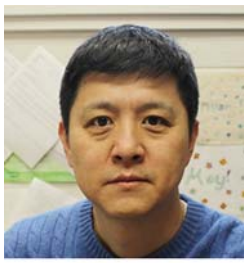

Jian Chen

Abstract: Chromatin structure regulating processes mediated by the adenosine triphosphate (ATP) – dependent chromatin remodeling complex and the covalent histone-modifying complexes are critical to gene transcriptional control and normal cellular processes, including cell stemness, differentiation, and proliferation. Gene mutations, structural abnormalities, and epigenetic modifications that lead to aberrant expression of chromatin structure regulating members have been observed in most of human malignancies. Advances in next-generation sequencing (NGS) technologies in recent years have allowed in-depth study of somatic mutations in human cancer samples. The Cancer Genome Atlas (TCGA) is the largest effort to date to characterize cancer genome using NGS technology. In this review, we summarize somatic mutations of chromatin-structure regulating genes from TCGA publications and other cancer genome studies, providing an overview of genomic alterations of chromatin regulating genes in human malignancies.

Keywords: Somatic mutation, Cancer, Chromatin structure, Chromatin remodeling, Chromatin modification, TCGA.

INTRODUCTION

Chromatin structure regulating processes are required for the structural changes of the chromatin, which allow protein complexes to access genomic DNA. These processes are essential for normal DNA-templated processes and functions, such as DNA transcription, synthesis and repair. Two major classes of enzymes are involved in chromatin structure regulating processes: 1) covalent histone-modifying enzymes, and 2) ATP-dependent chromatin remodeling enzymes [1].

The Cancer Genome Atlas (TCGA) project aims to discover major genomic alterations in human cancer, and create a comprehensive database of cancer genomic information. Through large-scale sequencing and multi-dimensional analyses, TCGA research network has sequenced and analyzed large numbers of tumor specimens from over 30 types of human cancers to discover molecular aberrations at the DNA, RNA, protein and epigenetic levels [2]. Our understanding of tumorigenesis has increased owing to TCGA group and individual analyses of cancers. The TCGA database can be assessed through the cBioPortal for Cancer Genomics (http://cbioportal.org), which is a Web portal for searching, visualizing, and analyzing multidimensional information of cancer genomics [3, 4]. In this review, we utilized the cBio portal complements existing tools and integrated genomic data from 36 cancer types (downloaded from http://cbioportal.org May 31, 2015) to summarize somatic mutations for key chromatin structure–regulating genes, and to provide an overview of genomic alterations of chromatin regulating genes in human malignancies.

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1. SOMATIC MUTATIONS IN CHROMATIN REMODELING GENES

There are four families of chromatin remodeling complexes identified in eukaryotes: SWI/SNF, ISWI, NuRD/CHD, and INO80. All the complexes share a common ATPase domain but they have specific functions on several biological processes based the unique protein domains (helicase, bromodomain, CHD domain, plant homeodomain, and SANT domain). All chromatin remodeling complexes share some similar characteristics: binding to nucleosomes; DNA-dependent ATPase activity; recognizing histone modification; regulating ATPase activity.

1.1 SWI/SNF Family Gene Mutations

Conserved from yeast to humans, the SWI/SNF (SWItching defective/Sucrose NonFermenting) complex comprises 10-15 biochemically distinct subunits. There are two distinct SWI/SNF complexes: Brahma-related gene 1–associated factor (BAF) and polybromo-associated BRG1-associated factor (PBAF) [5-8]. BAF complex include ARID1A (BAF250A), ARID1B (BAF250B), BRD9, SYT1, BCL7A, BCL7B, BCL7C, and SS18L1. However, PBRM1, ARID2 (BAF200), PHF10, BCL11A, BCL11B, and BRD7 are found in only the PBAF complex. There are also common subunits that are responsible for targeting, assembly, and regulation of SWI/SNF complex. They include SMARCB1 (BAF47/SNF5), SMARCA4, SMARCA2, SMARCC1 (BAF155), SMARCC2 (BAF170), SMARCE1 (BAF57), SMARCD1 (BAF60A), SMARCD2 (BAF60B) or

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SMARCD3 (BAF60C), DPF1 (BAF45B) or DPF2 (BAF45D), DPF3 (BAF45C), and ACTL6A (BAF53A) or ACTL6B (BAF53B). Analyses of cancer genomes show that the genes encoding SWI/SNF proteins are frequently mutated and inactivated in a variety of human cancers (Table **1**) [9, 10].

1.1.1. Mutations in BAF Complex Members

ARID1A (BAF250A) and ARID1B (BAF250B) are the main subunits of the SWI/SNF complex. ARID1A is one of the most frequently mutated genes among diverse cancers (Table **1**). The updated TCGA data demonstrate that ARID1A is mutated in in 18-31% of stomach adenocarcinomas [11-14], 15-27% of cholangiocarcinomas [15-17], 34% of uterine corpus endometrioid carcinomas [18], and similarly high rates in several other cancers [19-33] (Table **1**). ARID1A mutations have also been detected in acute myeloid Leukemia (0.5%) [34] and multiple myeloma (1%) [35]. ARID1A mutations seem to be more frequent in solid cancers, with a relatively high rate in gastrointestinal tract cancers and a relatively low rate in blood cancers. ARID1A is also mutated at low rates in various cancers, including breast carcinoma [36-39], clear cell renal carcinoma [40, 41], and ovarian serous cystadenocarcinoma [42]. Most ARID1A mutations detected in cancer cells to date are inactivating mutations, indicating that ARID1A has a tumor suppressive function.

The function of ARID1B in cancer remains unknown. However, ARID1B is frequently mutated in stomach adenocarcinoma (9%) [11-14], colorectal adenocarcinoma (4-7%) [19-20], melanoma (4-8%) [26-28] and lung cancer (10%) [29-32]. ARID1B is also mutated in a small fraction of patients with bladder urothelial carcinoma, breast invasive carcinoma, kidney renal clear cell carcinoma, esophageal adenocarcinoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, medulloblastoma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, papillary thyroid carcinoma, pancreatic adenocarcinoma, papillary thyroid carcinoma, and uterine corpus endometrioid carcinoma (Table **1**). SYT1 mutations are found in 5-11% of melanoma, suggesting that SYT1 may have a functional role in melanoma pathogenesis [26] (Table **1**). Other BAF complex genes, BRD9, BCL7A, BCL7B, BCL7C, and SS18L1 are mutated at low frequency in cancers.

1.1.2. Mutations Associated with the PBAF Complex

PBRM1, ARID2 (BAF200), PHF10, BCL11A, BCL11B and BRD7 subunits are found only in PBAF complex. ARID2 gene is mutated in various cancers, including in melanoma [26-28], stomach adenocarcinoma [11, 12], colorectal adenocarcinoma [19, 20], bladder urothelial carcinoma [23-25], liver hepatocellular carcinoma [21, 22], and lung cancer [29-32] at rates between 4% to 11% (Table **1**). ARID2 mutation was identified as a driver mutation in a large-scale melanoma whole exome sequencing study. In this study, ARID2 has a 7.4% mutation rate in malignant melanomas caused by exposure to ultraviolet light. Most of these ARID2 mutations were inactivating mutations [26].

PBRM1 is mutated in 36% of kidney renal clear cell carcinoma [41], which is the second most frequently mutated gene in renal cell carcinoma after VHL [40]. Five to six percent of stomach adenocarcinoma [11-13], and 6-7% of bladder urothelial carcinoma [23-25] harbor PBRM1 mutations in recent large-scale exome sequencing studies. Interestingly, PBRM1 mutations were also detected in 18% of intrahepatic cholangiocarcinoma [17]. Frequent alterations in BAP1, ARID1A and PBRM1, including inactivating, nonsense, frame shift and splice-site mutations in cholangiocarcinomas, highlight the key role of chromatin remodeling in this tumor type. Patients with mutations in one of these chromatin remodeling genes tended to have shorter survival times than those without mutations in these genes [17]. Notably, these mutations may be novel therapeutic targets cholangiocarcinomas, as the mutations may confer sensitivity to drugs targeting chromatin remodeling, such as histone deacetylase inhibitors, which are already in use or being developed for individuals with cancer.

PBAF complex-associated gene BCL11A has a 9.9% mutation rate in skin cutaneous melanoma [26] and 5-7% rate in stomach adenocarcinoma [12, 13], and BCL11B has 7-12% mutation rate in melanomas [26, 28] and a 9.7% mutation rate in colorectal adenocarcinoma [19] (Table **1**).

1.1.3. Mutations in Common Subunits of SWI/SNF

SMARCB1 is mutated in 5.6% of colorectal adenocarcinomas [19], 3.8% of stomach adenocarcinomas [12] , 3.7% of bladder cancers [24] and at lower mutation rates in other cancers (Table **1**). Although somatic mutations of SMARCB1 are rare in malignant rhabdoid tumors, an aggressive cancer typically occurring in young children, SMARCB1 is inactivated via biallelic genetic alterations in almost 95% of these cancers [43]. Thus, SMARCB1 appears to be a major driver gene for rhabdoid tumors.

Sequencing of the SMARCA4 gene shows that SMARCA4 is mutated in various cancers, including bladder urothelial carcinoma [23-25], cholangiocarcinoma [15], colorectal adenocarcinoma [19, 20], esophageal adenocarcinoma [44], lung cancer [29-32], medulloblastoma [45-47], melanoma [26-28], stomach adenocarcinoma [11-14] and uterine corpus endometrioid carcinoma [18] at rates between 4% and 13% (Table **1**). SMARCA4 mutations were also confirmed in lung adenocarcinoma by a large-scale genome analysis [29].

SMARCA2 is mutated in 5% of adenoid cystic carcinoma [48], 7% of bladder urothelial carcinoma [25], 6% of colorectal adenocarcinoma [19, 20], 7% of small cell Lung cancer [49], 6% of stomach adenocarcinoma [12] and 7% uterine corpus endometrioid carcinoma [18]. Loss of SMARCA2 expression levels developed an ethyl carbamate-induced lung tumor in mice [50]. Furthermore, low levels of SMARCA2 expression in non–small cell lung cancer correlates with a worse prognosis [51, 52]. These findings suggest that SMARCA2 is a tumor suppressor gene.

SMARCC1 (BAF155) is mutated in 6% of colorectal adenocarcinomas [19], 7% of small cell Lung cancers [49], 5% of stomach adenocarcinomas [12]. SMARCC2 (BAF170) is mutated in 4.6% of bladder urothelial carcinomas [25] and 5% of stomach adenocarcinomas [12]. SMARCD1 (BAF60A), SMARCD2 (BAF60B), and

Table 1. Mutations in SWI/SNF components reported in TCGA publications.

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
ACTL6A	Breast	Breast Cancer Patient Xenografts (British Columbia, Nature 2014)	8	116	6.9%
ACTL6B	Melanoma	Cutaneous Melanoma (Yale, Nature Genetics 2012)	4	91	4.4%
ACTB	Breast	Breast Cancer Patient Xenografts (British Columbia, Nature 2014)	7	29	24.1%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	24	286	8.4%
	Lung	Lung Adenocarcinoma (TCGA, Nature 2014)	18	231	7.8%
	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	9	127	7.1%
		Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013)	7	99	7.1%
	Adenoid	Adenoid Cystic Carcinoma (MSKCC, Nature Genetics 2013)	4	60	6.7%
	Nerve	Malignant Peripheral Nerve Sheath Tumor (MSKCC, Nature Genetics 2014)	1	15	6.7%
	Prostate	Prostate Adenocarcinoma, Metastatic (Michigan, Nature 2012)	4	61	6.6%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	8	182	4.4%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
ACTL6A	Breast	Breast Cancer Patient Xenografts (British Columbia, Nature 2014)	8	116	6.9%
ACTL6B	Melanoma	Cutaneous Melanoma (Yale, Nature Genetics 2012)	4	91	4.4%
ARID1A	Bladder	Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013)	15	99	15.2%
		Bladder Cancer (MSKCC, Eur Urol 2014)	31	109	28.4%
		Bladder Urothelial Carcinoma (TCGA, Nature 2014)	33	130	25.4%
	Cholangiocarci-noma	Intrahepatic Cholangiocarcinoma (Johns Hopkins Univer-sity, Nature Genetics 2013)	6	40	15.0%
		Cholangiocarcinoma (National Cancer Centre of Singapore, Nature Genetics 2013)	4	15	26.7%
		Cholangiocarcinoma (National University of Singa-pore,Nature Genetics 2012)	1	8	12.5%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	5	72	6.9%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	21	223	9.4%
	Esophagus	Esophageal Adenocarcinoma (Broad, Nature Genetics 2013)	13	146	8.9%
	Liver	Liver Hepatocellular Carcinoma (RIKEN, Nature Genetics 2012)	3	21	14.3%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	15	183	8.2%
		Lung Adenocarcinoma (TCGA, Nature 2014)	16	229	7.0%
		Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	2	42	4.8%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	14	121	11.6%
		Cutaneous Melanoma (Yale, Nature Genetics 2012)	7	91	7.7%

(Table 1) contd….

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
		Melanoma (Broad/Dana Farber, Nature 2012)	3	25	12.0%
	Pancreas	Pancreatic Adenocarcinoma (ICGC, Nature 2012)	4	100	4.0%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	18	100	18.0%
		Stomach Adenocarcinoma (TCGA, Nature 2014)	90	289	31.1%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	6	22	27.3%
		Stomach Adenocarcinoma (U Tokyo, Nature Genetics 2014)	5	30	16.7%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	83	248	33.5%
ARID1B	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	6	130	4.6%
	Breast	Breast Invasive Carcinoma (Sanger, Nature 2012)	5	100	5.0%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	5	72	6.9%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	9	225	4.0%
	Lung	Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)	3	29	10.3%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	5	122	4.1%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	27	290	9.3%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	2	22	9.1%
ARID2	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	12	130	9.2%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	15	224	6.7%
	Esophagus	Esophageal Adenocarcinoma (Broad, Nature Genetics 2013)	8	145	5.5%
	Lung	Lung Adenocarcinoma (TCGA, Nature 2014)	14	230	6.1%
		Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	2	42	4.8%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	11	121	9.1%
		Cutaneous Melanoma (Yale, Nature Genetics 2012)	10	91	11.0%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	5	100	5.0%
		Stomach Adenocarcinoma (TCGA, Nature 2014)	22	289	7.6%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	14	250	5.6%
BCL11A	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
	Glioblastoma	Glioblastoma (TCGA, Nature 2008)	4	91	4.4%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	8	182	4.4%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	12	121	9.9%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	19	288	6.6%

(Table 1) contd….

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
BCL11B	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	7	72	9.7%
	Melanoma	Skin Cutaneous Melanoma (Broad, Cell 2012)	8	121	6.6%
		Melanoma (Broad/Dana Farber, Nature 2012)	3	25	12.0%
HDAC1	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
HDAC2	Cholangiocarci-noma	Cholangiocarcinoma (National University of Singa-pore,Nature Genetics 2012)	1	8	12.5%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genet-ics 2014)	4	100	4.0%
PBRM1	Bladder	Bladder Cancer (MSKCC, Eur Urol 2014)	6	109	5.5%
		Bladder Urothelial Carcinoma (TCGA, Nature 2014)	9	130	6.9%
	Head & neck	Head and Neck Squamous Cell Carcinoma (Broad, Science 2011)	3	73	4.1%
	Cholangiocarci-noma	Intrahepatic Cholangiocarcinoma (Johns Hopkins Univer-sity, Nature Genetics 2013)	7	40	17.5%
	Kidney	Renal Clear Cell Carcinoma (TCGA, Nature 2013)	153	424	36.1%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	18	290	6.2%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	11	250	4.4%
SYT1	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	13	121	10.7%
		Cutaneous Melanoma (Yale, Nature Genetics 2012)	5	91	5.5%
		Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
SMARCA2	Adenoid	Adenoid Cystic Carcinoma (MSKCC, Nature Genetics 2013)	3	60	5.0%
	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	9	130	6.9%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
	Lung	Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)	2	29	6.9%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	18	290	6.2%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	17	246	6.9%
SMARCA4	Bladder	Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013)	5	98	5.1%
		Bladder Cancer (MSKCC, Eur Urol 2014)	10	109	9.2%
		Bladder Urothelial Carcinoma (TCGA, Nature 2014)	11	129	8.5%
	Cholangiocarci-noma	Cholangiocarcinoma (National Cancer Centre of Singapore, Nature Genetics 2013)	1	15	6.7%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	10	72	13.9%

(Table 1) contd….

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
	Esophagus	Esophageal Adenocarcinoma (Broad, Nature Genetics 2013)	10	147	6.8%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	20	183	10.9%
		Lung Adenocarcinoma (TCGA, Nature 2014)	13	228	5.7%
	Medulloblastoma	Medulloblastoma (Broad, Nature 2012)	4	93	4.3%
		Medulloblastoma (ICGC, Nature 2012)	6	113	5.3%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	11	121	9.1%
		Cutaneous Melanoma (Yale, Nature Genetics 2012)	5	91	5.5%
		Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	Ovary	Small Cell Carcinoma of the Ovary (MSKCC, Nature Genetics 2014)	11	12	91.7%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	9	100	9.0%
		Stomach Adenocarcinoma (TCGA, Nature 2014)	18	290	6.2%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	16	246	6.5%
SMARCB1	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	11	289	3.8%
SMARCC1	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
	Lung	Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)	2	29	6.9%
	Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
SMARCC2	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	6	130	4.6%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	14	292	4.8%
		Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	5	100	5.0%
	MPNST	Malignant Peripheral Nerve Sheath Tumor (MSKCC, Nature Genetics 2014)	1	15	6.7%
SMARCD1	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
SMARCD2	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	5	72	6.9%
SMARCD3	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%

Data from cell lines or single case reports were not included in the table. Mutation rates of less 4% are not presented. MPNST: malignant peripheral nerve sheath tumor.

SMARCD3 (BAF60C), are mutated in 5%, 6.9% and 4.2% of colorectal adenocarcinomas, respectively [19]. DPF1 (BAF45B), DPF2 (BAF45D) and DPF3 (BAF45C) are rarely identified in human cancers.

1.2. ISWI Family Gene Mutations

ISWI (Imitation SWItch) was discovered in a search for genes related the brahma (brm), a *Drosophila* relative of SWI/SNF2 [53, 54]. Homologues of ISWI complexes were later discovered in yeasts, plants, nematodes and humans, suggesting that ISWI complexes are highly conserved across species and play a conserved role in chromatin remodeling in eukaryotic cells [55-58]. Studies have shown that the ISWI complexes are involved in important nuclear functions such DNA replication, DNA repair, transcriptional regulation and chromosome structure maintenance [59-62].

1.2.1. ISWI Mutations are Common Across Diverse Cancer Types

SMARCA5 (ISWI or SNF2H) is the core ATPase subunit of ISWI complex, and mutated in 5.6% of colorectal adenocarcinomas [19] and 5.2% of uterine corpus endometrioid carcinomas [18]. The other catalytic ATPase subunit SMARCA1 (SNF2L) is mutated in 12.5% of cholangiocarcinomas [16], 7% of uterine corpus endometrioid carcinomas [18], 4% of colorectal adenocarcinomas [19] and 5% of stomach adenocarcinomas [11, 14] (Table **2**). BAZ1A (ACF1) is mutated in various cancers, including colorectal adenocarcinoma [19, 20], melanoma [28] and uterine corpus endometrioid carcinoma [18], at rates between 4% and 7% (Table **2**). BAZ1B (WSTF) is mutated in 5% of colorectal adenocarcinomas [19, 20], 7% of lung cancers [29, 30, 32] and 5.2% of uterine corpus endometrioid carcinomas [18]. BAZ2A (TIP5) is mutated in 6% of colorectal adenocarcinoma [19, 20], 5% of stomach adenocarcinoma [12] and 6.5% of uterine corpus endometrioid carcinoma [18]. CECR2 is mutated in various cancers, including melanoma [26, 28], lung squamous cell carcinoma [32], colorectal adenocarcinoma [19, 20], stomach adenocarcinoma [11, 12, 14] and uterine corpus endometrioid carcinoma [18], at rates between 5% and 16% (Table **2**). RBBP4 (RbAp48) is mutated in 4.8% of small cell lung cancers and 4.9% of prostate adenocarcinomas [31, 63]. RBBP7 (RbAp46) is mutated in 12.5% of cholangiocarcinoma [16]. RSF1is mutated in 4% of colorectal adenocarcinoma [19-20], 8% of melanoma [28] and 5-6% of stomach adenocarcinoma [11, 12, 14]. BPTF (NURF) is mutated in various cancers, including melanoma [26, 27], stomach adenocarcinoma [11, 14], lung cancer [29, 30, 32] and cholangiocarcinoma [16], at rates between 5% and 7% (Table **2**). These data suggest that ISWI family genes may also play a tumor suppressive role in diverse cancers (Table **2**).

1.3. CHD Family Gene Mutations

Much of the CHD (Chromodomain, Helicase, DNA binding) family proteins are highly conserved from yeast to humans [64, 65]. In human cells, the catalytic subunits of CHD chromatin remodelers are CHD1, CHD2, CHD6, CHD7, CHD8, and CHD9, whereas the core ATPase subunits of NuRD (Nucleosome Remodeling and Deacetylases) chromatin remodelers are CHD3 and CHD4 [1, 66]. The CHD proteins have established and emerging roles in DNA repair, the oxidative stress response, and the maintenance of genomic stability.

1.3.1. CHD1 and CHD2 Subfamily

TCGA data indicate that CHD1 is mutated in 4-10% of colorectal adenocarcinomas [19, 20], 9% of stomach adenocarcinomas [11-14], 4.4% of uterine corpus endometrioid carcinomas [18] and 5.4% of bladder urothelial carcinomas [25] (Table **3**). Recent study shows that mutations and deletion of CHD1 are found in approximately 17% local prostate cancers [67, 68]. These results also suggest that CHD1 plays a tumor suppressive role in cancers. Mutation of CHD2 in mice is lethal, demonstrating CHD2's importance in embryonic development [69]. $CHD2^{+/-}$ mice display susceptibility to lymphoma and alterations to their hematopoietic system, in which their stem cells differentiate abnormally. TCGA data indicate that CHD2 is mutated in 4-9% of bladder urothelial carcinoma [23, 25], 4-5% of colorectal adenocarcinoma [19, 20], 4-7% of stomach adenocarcinoma [11, 12, 14], and 6.5% of uterine corpus endometrioid carcinoma, suggesting that CHD2 also plays a tumor suppressive role in cancers [18] (Table **3**).

1.3.2. CHD3 and CHD4 Subfamily

CHD3 and CHD4 are the core ATPases of the NuRD complex. Depletion of CHD3 by siRNA in human cells indicates CHD is involved in ATM-mediated DNA repairs [70]. Our literature review shows that CHD3 is mutated in various cancers, including colorectal adenocarcinoma [19, 20], stomach adenocarcinoma [11-14] and prostate adenocarcinoma [71], at rates between 5% and 11% (Table **3**). Mutant CHD4 genes are found in 17% of human endometrial cancers and 20% of uterine serous carcinomas [72, 73]. CHD4 also has been shown to regulate DNA repair response and G1/S cell cycle transition [74]. TCGA data indicated that CHD4 is mutated in various cancers at rates between 5% and 14% (Table **3**). These results suggest that the core CHD complex CHD3/4 plays a tumor suppressive role and maintains chromosome stability.

1.3.3. CHD5-CHD9 Subfamily

The third CHD subfamily contains the proteins CHD5, CHD6, CHD7, CHD8, and CHD9. The updated TCGA data also show that CHD5 is mutated in 4% of head and neck squamous cell carcinomas [75] and 3-7% of melanomas [26, 27]. Mutations of CHD6 are found in human colorectal and bladder cancers [76, 77]. TCGA data also indicate that CHD6 is mutated in 12% colorectal adenocarcinomas [20], 10% of stomach adenocarcinomas [11] and 8.1% of uterine corpus endometrioid carcinomas [18]. CHD7 mutation is associated with lung cancer of heavy smokers [78]. In pancreatic cancer, low CHD7 expression predicts better survival rate in patients receiving adjuvant gemcitabine [79]. CHD7 is mutated in 10% of bladder urothelial carcinomas [25], 8.1% of medulloblastomas [47], and 8.1% of uterine corpus endometrioid carcinomas [18]. CHD8 expression is inhibited in prostate cancer tissues by promoter hypermethylation [80]. CHD8 is mutated in 9% of colorectal adenocarcinomas [20], and 7.7% of uterine corpus endometrioid carcinomas [18]. The role of CHD9 in cancer is still unclear. TCGA data show that CHD9 is mutated in various cancers, including in bladder urothelial carcinoma [25], colorectal adenocarcinoma [19-20], lung cancer [29-32], melanoma [26, 27], and

Table 2. Mutations in ISWI components reported in TCGA publications.

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
BAZ1A (ACF1)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	5	72	6.9%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	12	286	4.2%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	13	250	5.2%
BAZ1B (WSTF)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
	Lung	Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	3	42	7.1%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	13	250	5.2%
BAZ2A (TIP5)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	15	288	5.2%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	16	246	6.5%
CECR2	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
	Lung	Lung Squamous Cell Carcinoma (TCGA, Nature 2012)	8	178	4.5%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	11	121	9.1%
		Melanoma (Broad/Dana Farber, Nature 2012)	4	25	16.0%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	17	288	5.9%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	14	250	5.6%
RBBP4 (RbAP48)	Lung	Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	2	42	4.8%
	Prostate	Prostate Adenocarcinoma, Metastatic (Michigan, Nature 2012)	3	61	4.9%
RBBP7 (RbAP46)	Cholangiocarcinoma	Cholangiocarcinoma (National University of Singapore,Nature Genetics 2012)	1	8	12.5%
RSF1	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	17	288	5.9%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
SMARCA5 (ISWI, SNF2H)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	13	250	5.2%
SMARCA1 (SNF2L)	Cholangiocarcinoma	Cholangiocarcinoma (National University of Singapore,Nature Genetics 2012)	1	8	12.5%
	Colorectal	Colorectal Adenocarcinoma (TCGA, Nature 2012)	9	225	4.0%

(Table 2) contd….

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
	Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	18	247	7.3%
BPTF (NURF)	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	8	129	6.2%
	Cholangiocarcinoma	Cholangiocarcinoma (National Cancer Centre of Singapore, Nature Genetics 2013)	1	15	6.7%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	5	72	6.9%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	8	182	4.4%
		Lung Squamous Cell Carcinoma (TCGA, Nature 2012)	12	179	6.7%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
		Cutaneous Melanoma (Broad, Cell 2012)	9	122	7.4%
		Cutaneous Melanoma (Yale, Nature Genetics 2012)	5	91	5.5%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	5	100	5.0%
		Stomach Adenocarcinoma (TCGA, Nature 2014)	18	290	6.2%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	20	247	8.1%

Data from cell lines or single case reports were not included in the table. Mutation rates of less 4% are not presented.

6.9% of uterine corpus endometrioid carcinoma [18], at rates between 4% and 10% (Table **3**),suggesting that CHD9 may also play a tumor suppressive role in diverse cancers (Table **3**).

1.4. INO80 and SWR1 Family Gene Mutations

The INO80 (INOsitol requiring 80) and SWR1 (Swi2/Snf2-Related) subfamily are the most recent addition to the SWI/SNF family of chromatin remodelers. INO80 complex is involved in gene transcription, DNA replication, chromosome segregation, and DNA repair [81-83].

1.4.1. INO80 Family Genes

INO80 family genes, including INO80, INO80B (Ies2), INO80C (Ies6), INO80D (FLJ20309), INO80E (CCDC95), NFRKB (INO80G), ACTL6A (INO80K), MCRS1 (INO80Q), UCHL5 (INO80R), and YY1 (INO80S), are not frequently mutated in cancers. INO80 is mutated in 9% (11/129) of bladder urothelial carcinomas [25], 7-8% of melanomas [26-28]. INO80D (FLJ20309) is mutated in 5% of stomach adenocarcinomas [11, 12], MCRS1 (INO80Q) is mutated in 5% of stomach adenocarcinomas [11, 12], NFRKB (INO80G) is mutated in 5.6% (4/71) of colorectal adenocarcinomas [19] and 6.9% (2/29) of small cell lung cancers [49]. RUVBL1 (RVB1) and RUVBL2 (RVB2) is mutated in several cancer types with low frequency (<4%). Actin-related proteins, ACTB (Beta-actin), ACTN4, ACTR3B (Arp4), ACTR5 (Arp5), ACTR6 (Arp6), ACTR8 (Arp8) are also rarely mutated in cancers (Table **4**).

1.4.2. SWR1 Family Genes

The SWR1 complex, a yeast counterpart to the human NuA4complex, is known to mediate the exchange of H2A for H2AZ, an essential H2A variant that defines border regions between heterochromatin and euchromatin, limiting the spread of hetero-chromatin into transcriptionally active regions [84, 85]. In SWR1 subcomplex, SRCAP (Swr1) is frequently mutated in melanomas [26-28], lung cancers [29-32], stomach adenocarcinoma [11-14], bladder urothelial carcinoma [23-25], colorectal adenocarcinoma [19, 20], uterine corpus endometrioid carcinoma [18] and nasopharyngeal carcinoma [86] at rates between about 5% and 10% (Table **4**). ERCC5 is mutated in 4-8% of melanomas [26-28] and 4% of stomach adenocarcinomas [11-14]. These data suggest that SRCAP and ERCC5may play specific roles in DNA repair or chromosome stability in cancer development. SRCAP may also be a potential cancer therapeutic target.

2. HISTONE MODIFICATION ENZYMES

Histone modifications are involved in numerous cellular chromatin-based processes, such as gene transcription, DNA repair, DNA replication, DNA recombination and chromosome segregation. Therefore, the aberrant histone modification profiles, or the dysregulated activity of the histone modifying enzymes may cause cancer by altering gene expression of oncogenes or tumor suppressors, and affecting genome integrity and chromosome segregation. Histone modifications consist of acetylation, methylation, phosphory-

Table 3. Mutations in CHD components reported in TCGA publications.

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
CHD1	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	7	130	5.4%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	7	72	9.7%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	9	225	4.0%
	Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	2	22	9.1%
CDH2	Bladder	Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013)	4	100	4.0%
		Bladder Urothelial Carcinoma (TCGA, Nature 2014)	12	130	9.2%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	10	222	4.5%
		Colorectal Adenocarcinoma (TCGA, Provisional)	10	222	4.5%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	7	100	7.0%
		Stomach Adenocarcinoma (TCGA, Nature 2014)	12	286	4.2%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	16	246	6.5%
CHD3	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	6	130	4.6%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	7	72	9.7%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	10	222	4.5%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	4	100	4.0%
		Stomach Adenocarcinoma (TCGA, Nature 2014)	19	288	6.6%
		Stomach Adenocarcinoma (TCGA, Provisional)	14	222	6.3%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	2	22	9.1%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	26	248	10.5%
CHD4	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	9	130	6.9%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	17	224	7.6%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	4	182	2.2%
		Lung Adenocarcinoma (TCGA, Nature 2014)	6	231	2.6%
		Lung Squamous Cell Carcinoma (TCGA, Nature 2012)	11	177	6.2%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
		Cutaneous Melanoma (Broad, Cell 2012)	11	121	9.1%
		Cutaneous Melanoma (Yale, Nature Genetics 2012)	6	91	6.6%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	26	289	9.0%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	35	248	14.1%
CDH5	Head & neck	Head and Neck Squamous Cell Carcinoma (Broad, Science 2011)	3	73	4.1%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%

(Table 3) contd…..

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
		Cutaneous Melanoma (Broad, Cell 2012)	9	122	7.4%
CDH6	Bladder	Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013)	5	98	5.1%
		Bladder Urothelial Carcinoma (TCGA, Nature 2014)	10	130	7.7%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	9	72	12.5%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	16	225	7.1%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	9	184	4.9%
		Lung Adenocarcinoma (TCGA, Nature 2014)	13	228	5.7%
		Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)	2	29	6.9%
		Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	2	42	4.8%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	11	121	9.1%
		Cutaneous Melanoma (Yale, Nature Genetics 2012)	6	91	6.6%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
	Prostate	Prostate Adenocarcinoma, Metastatic (Michigan, Nature 2012)	3	61	4.9%
		Metastatic Prostate Cancer, SU2C/PCF Dream Team (Robinson *et al.*, Cell 2015)	6	150	4.0%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	29	290	10.0%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	20	247	8.1%
CDH7	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	13	130	10.0%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	7	72	9.7%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	9	225	4.0%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	11	183	6.0%
		Lung Adenocarcinoma (TCGA, Nature 2014)	12	231	5.2%
		Lung Squamous Cell Carcinoma (TCGA, Nature 2012)	13	178	7.3%
	Medulloblastoma	Medulloblastoma (PCGP, Nature 2012)	3	37	8.1%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	6	120	5.0%
		Melanoma (Broad/Dana Farber, Nature 2012)	3	25	12.0%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	5	100	5.0%
		Stomach Adenocarcinoma (TCGA, Nature 2014)	27	290	9.3%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	20	247	8.1%
CDH8	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	7	72	9.7%
	Esophagus	Esophageal Adenocarcinoma (Broad, Nature Genetics 2013)	6	146	4.1%
	Head & neck	Head and Neck Squamous Cell Carcinoma (Broad, Science 2011)	3	73	4.1%
	Lung	Lung Adenocarcinoma (TCGA, Nature 2014)	12	231	5.2%
		Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	3	42	7.1%
		Lung Squamous Cell Carcinoma (TCGA, Nature 2012)	10	179	5.6%

(Table 3) contd…..

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	8	121	6.6%
		Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
	Prostate	Prostate Adenocarcinoma, Metastatic (Michigan, Nature 2012)	3	61	4.9%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	17	288	5.9%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	19	247	7.7%
CDH9	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	8	129	6.2%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	6	72	8.3%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	11	224	4.9%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	13	183	7.1%
		Lung Adenocarcinoma (TCGA, Nature 2014)	10	233	4.3%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	7	121	5.8%
		Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	16	291	5.5%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	17	246	6.9%

Data from cell lines or single case reports were not included in the table. Mutation rates of less 4% are not presented.

Table 4. Mutations inINO80/SWR1 components reported in TCGA publications.

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
SRCAP (Swr1)	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	13	130	10.0%
	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
		Colorectal Adenocarcinoma (TCGA, Nature 2012)	14	222	6.3%
	Head & neck	Head and Neck Squamous Cell Carcinoma (Broad, Science 2011)	3	73	4.1%
	Lung	Lung Adenocarcinoma (Broad, Cell 2012)	14	182	7.7%
		Lung Adenocarcinoma (TCGA, Nature 2014)	13	228	5.7%
		Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	5	42	11.9%
		Lung Squamous Cell Carcinoma (TCGA, Nature 2012)	13	178	7.3%
	Melanoma	Skin Cutaneous Melanoma (Broad, Cell 2012)	15	121	12.4%
		Skin Cutaneous Melanoma (Yale, Nature Genetics 2012)	6	91	6.6%
		Melanoma (Broad/Dana Farber, Nature 2012)	4	25	16.0%
	Nasopharyngeal	Nasopharyngeal Carcinoma (Singapore, Nature Genetics 2014)	3	56	5.4%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	8	100	8.0%
		Stomach Adenocarcinoma (TCGA, Nature 2014)	32	288	11.1%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	19	247	7.7%

(Table 4) contd…

Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
INO80	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	11	129	8.5%
	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	8	121	6.6%
		Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	15	288	5.2%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
ERCC5	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
	Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	4	100	4.0%
		Stomach Adenocarcinoma (TCGA, Nature 2014)	14	292	4.8%
		Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	11	250	4.4%
ACTR5 (Arp5)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
NFRKB (INO80G)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
	Lung	Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)	2	29	6.9%
INO80D (FLJ20309)	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	13	289	4.5%
MCRS1 (INO80Q)	Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
RUVBL2 (RVB2)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
ACTR6 (Arp6)	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
CFDP1 (Swc5)	Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
ACTN4	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	5	122	4.1%

Data from cell lines or single case reports were not included in the table. Mutation rates of less 4% are not presented.

lation, ubiquitination, sumoylation biotination, citrullination, poly-ADP-ribosylation, and N-glycosylation. Here we review the major mutations of histone modification enzymes that have been identified in human cancers.

2.1. Mutations in Histone Acetylation and Deacetylation Enzymes

2.1.1. Histone Acetyltransferases (HATs)

Mutations of lysine acetyltransferases (KAT) family KAT8 (MYST1) have been reported many cancers (Table **5**). KAT6A (MYST3) and KAT6B (MYST4) are most frequently mutated in diverse cancers, including malanoma, colorectal adenocarcinoma and stomach adenocarcinoma (Table **5**). KAT8 (MYST1), KAT7 (MYST2) and KAT2B (PCAF) are mutated occasionally in cancers. Reports show that KAT5 (Tip60) interacts with p53 and E2F1 to activate tumor suppressor gene expression for DNA repair and apoptosis in malanoma and lung cancer [87-90]. However, KAT5 mutations were found in only 9.1% (2/22, missense) in stomach adenocarcinoma [13] (Table **5**). GNAT1 is an HAT which transfers an acyl group to the N-terminus of glutamine. GNAT1 mutations were found in 6-12% of melanomas [26-28] and 4.8% of small cell of lung cancers [31].

EP300 (p300) promotes cancer progression in colon, lung and prostate cancers [91-93]. Knockdown of EP300 induces cell apoptosis in prostate cancer cells [94]. The nonsense mutation, homozygous deletion and fragmental insertion mutation of EP300 are found in 14-16% of bladder cancers [23-25] as well as other different cancers (Table **5**). In acute myeloid leukemia (AML), recurrent genomic translocations fuse MLL gene fuses with CBP t (11,16) and p300 t (11,22) gene [95, 96]. These findings suggest that EP300 is a tumor suppressor gene.

Table 5. Mutations in histone modification components reported in TCGA publications.

Subgroup	Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
Histone acetyl-transferases	KAT8 (MYST1)	Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	2	22	9.1%
	KAT7 (MYST2)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
		Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	KAT6A (MYST3)	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	6	130	4.6%
		Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
			Colorectal Adenocarcinoma (TCGA, Nature 2012)	11	224	4.9%
		Esophagus	Esophageal Adenocarcinoma (Broad, Nature Genetics 2013)	8	145	5.5%
		Lung	Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)	2	29	6.9%
			Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	2	42	4.8%
			Lung Squamous Cell Carcinoma (TCGA, Nature 2012)	10	179	5.6%
		Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	11	121	9.1%
			Cutaneous Melanoma (Yale, Nature Genetics 2012)	4	91	4.4%
			Melanoma (Broad/Dana Farber, Nature 2012)	3	25	12.0%
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	22	289	7.6%
			Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	15	250	6.0%
	KAT6B (MYST4)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	7	72	9.7%
			Colorectal Adenocarcinoma (TCGA, Nature 2012)	9	225	4.0%
		Lung	Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)	2	29	6.9%
		Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	12	121	9.9%
			Cutaneous Melanoma (Yale, Nature Genetics 2012)	5	91	5.5%
			Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
		Prostate	Prostate Adenocarcinoma, Metastatic (Michigan, Nature 2012)	3	61	4.9%

(Table 5) contd….

Subgroup	Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	17	288	5.9%
			Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	2	22	9.1%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	15	250	6.0%
	KAT2B (PCAF)	Lung	Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	2	42	4.8%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	10	250	4.0%
	KAT5 (Tip60)	Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	2	22	9.1%
	GLYATL1	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	3	25	12.0%
			Cutaneous Melanoma (Broad, Cell 2012)	12	121	9.9%
			Cutaneous Melanoma (Yale, Nature Genetics 2012)	6	91	6.6%
		Lung	Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	2		4.8%
	EP300	Bladder	Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013)	14	99	14.1%
			Bladder Cancer (MSKCC, Eur Urol 2014)	17	109	15.6%
			Bladder Urothelial Carcinoma (TCGA, Nature 2014)	20	130	15.4%
		Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	10	72	13.9%
			Colorectal Adenocarcinoma (TCGA, Nature 2012)	12	222	5.4%
		Lung	Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)	2	29	6.9%
			Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	4	42	9.5%
		Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	7	121	5.8%
			Cutaneous Melanoma (Yale, Nature Genetics 2012)	4	91	4.4%
			Melanoma (Broad/Dana Farber, Nature 2012)	2	25	8.0%
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	18	290	6.2%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	21	247	8.5%
	KMT2A (MLL)	AML	Acute Myeloid Leukemia (TCGA, NEJM 2013)	10	200	5.0%

(Table 5) contd….

Subgroup	Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
		Bladder	Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013)	8	99	8.1%
			Bladder Cancer (MSKCC, Eur Urol 2014)	12	109	11.0%
			Bladder Urothelial Carcinoma (TCGA, Nature 2014)	18	130	13.8%
		Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	7	72	9.7%
			Colorectal Adenocarcinoma (TCGA, Nature 2012)	13	224	5.8%
		Esophageal	Esophageal Adenocarcinoma (Broad, Nature Genetics 2013)	6	146	4.1%
		Liver	Liver Hepatocellular Carcinoma (AMC, Hepatology 2014)	10	233	4.3%
		Lung	Lung Adenocarcinoma (Broad, Cell 2012)	9	184	4.9%
			Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)	3	29	10.3%
		Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	14	121	11.6%
			Cutaneous Melanoma (Yale, Nature Genetics 2012)	8	91	8.8%
			Melanoma (Broad/Dana Farber, Nature 2012)	3	25	12.0%
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	33	289	11.4%
			Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	18	247	7.3%
	RUNX1 (AML1)	AML	Acute Myeloid Leukemia (TCGA, NEJM 2013)	27	200	13.5%
		MPNST	Malignant Peripheral Nerve Sheath Tumor (MSKCC, Nature Genetics 2014)	1	15	6.7%
Histone deacetylases	HDAC1	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	HDAC2	Cholangiocarcinoma	Cholangiocarcinoma (National University of Singapore,Nature Genetics 2012)	1	8	12.5%
		Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
		Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	4	100	4.0%
		Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%

(Table 5) contd….

Subgroup	Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
Histone lysine methyltrans-ferases	EZH2	AML	Acute Myeloid Leukemia (TCGA, NEJM 2013)	8	29	27.6%
		Bladder	Bladder Cancer (MSKCC, Eur Urol 2014)	3	30	10.0%
			Bladder Urothelial Carcinoma (TCGA, Nature 2014)	4	41	9.7%
		Breast	Breast Invasive Carcinoma (TCGA, Nature 2012)	4	63	6.3%
		Kidney	Renal Clear Cell Carcinoma (TCGA, Nature 2013)	4	69	5.8%
		Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	2	37	5.4%
			Colorectal Adenocarcinoma (TCGA, Nature 2012)	4	74	5.4%
		Esophagus	Esophageal Adenocarcinoma (Broad, Nature Genetics 2013)	3	59	5.1%
			Esophageal Squamous Cell Carcinoma (ICGC, Nature 2014)	1	20	5.0%
		Glioblastoma	Glioblastoma (TCGA, Cell 2013)	6	122	4.9%
		Head & neck	Head and Neck Squamous Cell Carci-noma (Broad, Science 2011)	3	67	4.5%
		Liver	Liver Hepatocellular Carcinoma (AMC, Hepatology 2014)	2	47	4.3%
		Lung	Lung Adenocarcinoma (Broad, Cell 2012)	1	23	4.3%
			Lung Adenocarcinoma (TCGA, Nature 2014)	10	238	4.2%
			Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	1	24	4.1%
			Lung Squamous Cell Carcinoma (TCGA, Nature 2012)	5	125	4.0%
	EHMT1	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
		Lung	Small Cell Lung Cancer (CLCGP, Na-ture Genetics 2012)	2	29	6.9%
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	13	289	4.5%
			Stomach Adenocarcinoma (UHK, Na-ture Genetics 2011)	1	22	4.5%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	12	250	4.8%
	EHMT2	Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	5	122	4.1%
		MPNST	Malignant Peripheral Nerve Sheath Tumor (MSKCC, Nature Genetics 2014)	1	15	6.7%

(Table 5) contd….

Subgroup	Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	12	286	4.2%
	DOT1L	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	6	130	4.6%
		Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	8	72	11.1%
		Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	7	121	5.8%
			Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	NSD1	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	7	130	5.4%
		Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	5	72	6.9%
		Head & neck	Head and Neck Squamous Cell Carcinoma (Broad, Science 2011)	7	74	9.5%
		Lung	Lung Squamous Cell Carcinoma (TCGA, Nature 2012)	11	177	6.2%
		Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	9	122	7.4%
		Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
		Prostate	Metastatic Prostate Cancer, SU2C/PCF Dream Team (Robinson *et al.*, Cell 2015)	6	150	4.0%
		Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	5	100	5.0%
			Stomach Adenocarcinoma (TCGA, Nature 2014)	18	290	6.2%
			Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	2	22	9.1%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	24	247	9.7%
	WHSC1 (NSD2)	Bladder	Bladder Urothelial Carcinoma (TCGA, Nature 2014)	7	130	5.4%
		Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	7	72	9.7%
		Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	10	120	8.3%
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	16	291	5.5%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	12	250	4.8%
Protein arginine methyltransferases	CARM1 (PRMT4)	Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	PRMT5	Head & neck	Head and Neck Squamous Cell Carcinoma (Broad, Science 2011)	3	73	4.1%

(Table 5) contd….

Subgroup	Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
	PRMT6	Cholangiocarcinoma	Cholangiocarcinoma (National University of Singapore,Nature Genetics 2012)	1	8	12.5%
	PRMT7	Cholangiocarcinoma	Cholangiocarcinoma (National Cancer Centre of Singapore, Nature Genetics 2013)	1	15	6.7%
	PRMT8	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
		Lung	Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	3	42	7.1%
	PRMT9	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
Histone demethylases	KDM2B	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	5	72	6.9%
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	18	290	6.2%
	KDM4C (GASC1)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
		Melanoma	Cutaneous Melanoma (Yale, Nature Genetics 2012)	4	91	4.4%
		Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	KDM4A	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
	KDM5B	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	6	72	8.3%
			Colorectal Adenocarcinoma (TCGA, Nature 2012)	9	225	4.0%
		Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	3	25	12.0%
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	14	292	4.8%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	15	250	6.0%
	KDM6A	ACyC	Adenoid Cystic Carcinoma (MSKCC, Nature Genetics 2013)	4	60	6.7%
		Bladder	Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013)	32	99	32.3%
			Bladder Cancer (MSKCC, Eur Urol 2014)	45	109	41.3%
			Bladder Urothelial Carcinoma (TCGA, Nature 2014)	31	130	23.8%
		Lung	Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)	2	42	4.8%
		Medulloblastoma	Medulloblastoma (ICGC, Nature 2012)	5	114	4.4%

(Table 5) contd….

Subgroup	Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
			Medulloblastoma (PCGP, Nature 2012)	3	37	8.1%
		Stomach	Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)	6	100	6.0%
			Stomach Adenocarcinoma (TCGA, Nature 2014)	12	286	4.2%
			Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	11	250	4.4%
	KDM1B (LSD2)	Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	13	289	4.5%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	13	250	5.2%
Other histone modification enzymes	RPS6KA5 (MSK1)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
		Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
		Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	RPS6KA4 (MSK2)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
		Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	7	121	5.8%
	AURKB	Melanoma	Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
		Stomach	Stomach Adenocarcinoma (UHK, Nature Genetics 2011)	1	22	4.5%
	BMI1 (Bmi-1)	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%
	BAP1	Kidney	Renal Clear Cell Carcinoma (BGI, Nature Genetics 2012)	7	81	8.6%
			Renal Clear Cell Carcinoma (TCGA, Nature 2013)	37	425	8.7%
		Cholangiocarcinoma	Intrahepatic Cholangiocarcinoma (Johns Hopkins University, Nature Genetics 2013)	7	40	17.5%
			Cholangiocarcinoma (National Cancer Centre of Singapore, Nature Genetics 2013)	4	15	26.7%
		NPC	Nasopharyngeal Carcinoma (Singapore, Nature Genetics 2014)	3	56	5.4%
		Stomach	Stomach Adenocarcinoma (TCGA, Nature 2014)	12	286	4.2%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	10	250	4.0%

(Table 5) contd….

Subgroup	Gene	Cancer type	Data source	No. of mutations	No. of total	% of mutations
	RNF20	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	4	71	5.6%
		Melanoma	Cutaneous Melanoma (Broad, Cell 2012)	6	120	5.0%
			Melanoma (Broad/Dana Farber, Nature 2012)	1	25	4.0%
		Uterine	Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)	12	250	4.8%
	RNF40	Colorectal	Colorectal Adenocarcinoma (Genentech, Nature 2012)	3	71	4.2%

Data from cell lines or single case reports were not included in the table. Mutation rates of less 4% are not presented.
AML: acute myeloid leukemia, MPNST: malignant peripheral nerve sheath tumor, ACyC: adenoid cystic carcinoma.

2.1.2. Histone Deacetylases (HDACs)

HDACs are generally divided into HDAC1, HDAC2 and HDAC3 subfamily, which reverse histone acetylation. The function of HDACs in different cancer types is complex. HDACs knockout mice indicate that histone deacetylases are tumor suppressors [97, 98]. However, in AML and acute promyelocytic leukemia (PML), HDACs interact with fusion protein AML1-ETO or PML-RARα and PLZF- RARα that were formed by chromosome translocation, indicating that HDACs are oncogenic protein [99-101]. Recently, several HDAC inhibitors have been approved to treat haematological tumours [102]. Mutation analyses of histone deacetylases show that HDAC1 and HDAC2 are mutated occasionally in cancers (Table **5**).

2.2. Mutations in Histone Methylation and Demethylation Enzymes

Histone methylation activates or represses transcription depending on the position of modifications and the number of attached methyl groups. Methylation states are controlled by two enzyme families: histone methyltransferases and histone demethylase.

2.2.1. Histone Methyltransferases (HMTs)

HMTs include histone lysine methyltransferases (HKMTs) family and protein arginine methyltransferases (PRMTs) family. EZH2 is a member of the EZH family of HKMTs, and is responsible for H3K27 methylation and transcription repression in the multi-subunit protein complex PRC2 (Polycomb Repressive Complex 2). Updated TCGA data indicate that EZH2 also is frequently mutated in AML (27,6%) and is mutated in several solid cancers, including bladder, lung and GI tract cancers at rates between 4% and 10% (Table **5**). However, recent results have shown that gain-of-function mutants within the EZH2 catalytic domain exist in germinal center B-cell–like diffuse large B-cell lymphomas, follicular lymphomas and melanomas [103-105].

EHMT1 and EHMT2 are H3K9-specific methyltransferases in the SUV39 group and are overexpressed in lung and bladder cancers [106-108]. Both EHMT1 and EHMT2 are mutated in stomach cancers at rates of 4-5% (Table **5**) [12]. DOT1L is another member of the HMTs family, which specifically mono-, di- and tri-methylates H3K79. TCGA data indicate that DOT1L is mutated in 11.1% of colorectal cancer , 4.6% of bladder cancer, and 5.8% of melanoma, suggesting that the tumor suppressive role of DOT1L in these cancers [109, 110].

NSD1 and WHSC1 (NSD2) are histone lysine methyltransferases in the SET2 subfamily that mediate H3K36 dimethylation. In acute myeloid leukemia, NSD1 forms a fusion protein with nucleoporin-98 in the recurring t(5;11)(q35;p15.5) genomic translocation [111, 112]. Both NSD1 and NSD2 are mutated in several cancers at rates of 4-10% (Table **5**).

Protein arginine methyltransferases include nine family members, PRMT1-9, many of which are associated with various cancers [113]. However, TCGA data indicate that protein arginine methyltransferases have few mutations in cancers.

2.2.2. Histone Demethylases (HDMs)

HDMs can be classified into two groups: Jumonji (JmjC)-domain groups and lysine specific demethylase 1 or 2 (LSD1/KDM1A and LSD2/KDM1B). JmjC-domain HDMs KDM2B, KDM4C (GASC1), KDM4A and KDM5B are overexpressed in many cancers suggesting their oncogenic function [114-120]. However, KDM2B is mutated in 6.2% (18/290) of stomach cancers and KDM5B is mutated in 4.8% (14/292) of stomach cancers and 6% (15/250) of uterine corpus endometrioid carcinoma. KDM6A antagonizes EZH2-mediated H3K27 methylation, and is mutated in bladder cancers, renal cell carcinomas, multiple myeloma, and T-cell acute lymphoblastic leukemia [121, 122]. TCGA data indicated that KDM6A is mutated in bladder urothelial carcinoma at a frequency of 23-41% [23-25], suggesting KDM6A may be a potential therapeutic target for bladder cancer (Table **5**).

LSD1 is highly expressed in prostate, lung, colorectal, and breast cancer and in neuroblastoma and also is associated with poor prognosis in these tumors [123]. However, TCGA data show that LSD1or LSD2 is rarely mutated in cancers (< 4%).

2.3. Mutations in Other Histone Modification Enzymes

Other histone modifications including histone phosphorylation, ubiquitination, sumoylation and poly-ADP-ribosylation, have been observed on H1, H2B, H3, and histone variant H2AX. They have important functions in DNA repair, mitosis and gene regulation [124]. Many mutations of these histone modification enzymes are observed in cancers, and involved in different molecular pathways regulate cell proliferation, differentiation, and cell death (Table **5**). BAP1 (BRCA1-associated protein 1) is an enzyme that removes ubiquitins from histone H2AX, changing the expression of specific genes Loss of BAP1 is involved in melanoma. BAP1 mutations are also found to mesothelioma, renal cell carcinoma, and other cancer types [125]. TCGA data indicate that BAP1 is mutated in 18-27% of cholangiocarcinoma [15, 17], proving a new therapeutic target for this lethal cancer (Table **5**).

CONCLUSIONS

Both covalent histone-modifying enzymes and ATP-dependent chromatin remodeling enzymes are critical to chromatin structure regulating processes that are involved in the regulation of gene transcription, DNA replication, DNA repair response, and chromatin stability. Aberrant gene expression due to loss of chromatin regulating complex function results in tumor development.

In this review, we overviewed the somatic mutations in chromatin regulating genes in human cancers based on TCGA large-scale genome sequencing and publicly available data. The large number of cancers harbored chromatin regulating gene mutations, suggesting a prevalent role for these genes in tumor suppression. Elucidation of the association between chromatin regulating gene mutations and the clinical therapeutic outcome may have possible broad relevance in cancer therapies. The mutation analysis may contribute to the expansion of knowledge of cancer genetic and epigenetic profiles, identifying potential cancer biomarkers and novel targets for anticancer strategies. In the future, the studies of cancer genomics could translate into cancer therapeutics and diagnostics, providing a great opportunity to develop personalized cancer medicine.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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REFERENCES

[1] Clapier, C.R.; Cairns, B.R. The biology of chromatin remodeling complexes. *Ann. Rev. Biochem.,* **2009**, *78*, 273-304.

[2] Tomczak, K.; Czerwinska, P.; Wiznerowicz, M. The Cancer Genome Atlas (TCGA): an immeasurable source of knowledge. *Contemporary Oncol.,* **2015**, *19*(1A), A68-77.

[3] Gao, J.; Aksoy, B.A.; Dogrusoz, U.; Dresdner, G.; Gross, B.; Sumer, S.O.; Sun, Y.; Jacobsen, A.; Sinha, R.; Larsson, E.; Cerami, E.; Sander, C.; Schultz, N. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci. Signal.,* **2013**, *6*(269), pl1.

[4] Cerami, E.; Gao, J.; Dogrusoz, U.; Gross, B.E.; Sumer, S.O.; Aksoy, B.A.; Jacobsen, A.; Byrne, C.J.; Heuer, M.L.; Larsson, E.; Antipin, Y.; Reva, B.; Goldberg, A.P.; Sander, C.; Schultz, N. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.,* **2012**, *2*(5), 401-404.

[5] Wilson, B.G.; Roberts, C.W. SWI/SNF nucleosome remodellers and cancer. *Nat. Rev. Cancer,* **2011**, *11*(7), 481-92.

[6] Euskirchen, G.; Auerbach, R.K.; Snyder, M. SWI/SNF chromatin-remodeling factors: multiscale analyses and diverse functions. *J. Biol. Chem.,* **2012**, *287*(37), 30897-30905.

[7] Wu, S.; Ge, Y.; Huang, L.; Liu, H.; Xue, Y.; Zhao, Y. BRG1, the ATPase subunit of SWI/SNF chromatin remodeling complex, interacts with HDAC2 to modulate telomerase expression in human cancer cells. *Cell Cycle,* **2014**, *13*(18), 2869-2878.

[8] Reisman, D.; Glaros, S.; Thompson, E.A. The SWI/SNF complex and cancer. *Oncogene,* **2009**, *28*(14), 1653-1668.

[9] Helming, K.C.; Wang, X.; Roberts, C.W. Vulnerabilities of mutant SWI/SNF complexes in cancer. *Cancer Cell,* **2014**, *26*(3), 309-317.

[10] Biegel, J.A.; Busse, T.M.; Weissman, B.E. SWI/SNF chromatin remodeling complexes and cancer. *Am. J. Med. Genet. C Semin. Med. Genet.,* **2014**, *166C*(3), 350-366.

[11] Wang, K.; Yuen, S.T.; Xu, J.; Lee, S.P.; Yan, H.H.; Shi, S.T.; Siu, H.C.; Deng, S.; Chu, K.M.; Law, S.; Chan, K.H.; Chan, A.S.; Tsui, W.Y.; Ho, S.L.; Chan, A.K.; Man, J.L.; Foglizzo, V.; Ng, M.K.; Chan, A.S.; Ching, Y.P.; Cheng, G.H.; Xie, T.; Fernandez, J.; Li, V.S.; Clevers, H.; Rejto, P.A.; Mao, M.; Leung, S.Y. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. *Nat. Genet.,* **2014**, *46*(6), 573-582.

[12] Cancer Genome Atlas Research, N. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature,* **2014**, *513*(7517), 202-209.

[13] Wang, K.; Kan, J.; Yuen, S.T.; Shi, S.T.; Chu, K.M.; Law, S.; Chan, T.L.; Kan, Z.; Chan, A.S.; Tsui, W.Y.; Lee, S.P.; Ho, S.L.; Chan, A.K.; Cheng, G.H.; Roberts, P.C.; Rejto, P.A.; Gibson, N.W.; Pocalyko, D.J.; Mao, M.; Xu, J.; Leung, S.Y. Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer. *Nat. Genet.,* **2011**, *43*(12), 1219-1223.

[14] Kakiuchi, M.; Nishizawa, T.; Ueda, H.; Gotoh, K.; Tanaka, A.; Hayashi, A.; Yamamoto, S.; Tatsuno, K.; Katoh, H.; Watanabe, Y.; Ichimura, T.; Ushiku, T.; Funahashi, S.; Tateishi, K.; Wada, I.; Shimizu, N.; Nomura, S.; Koike, K.; Seto, Y.; Fukayama, M.; Aburatani, H.; Ishikawa, S. Recurrent gain-of-function mutations of RHOA in diffuse-type gastric carcinoma. *Nat. Genet.,* **2014**, *46*(6), 583-7.

[15] Chan-On, W.; Nairismagi, M.L.; Ong, C.K.; Lim, W.K.; Dima, S.; Pairojkul, C.; Lim, K.H.; McPherson, J.R.; Cutcutache, I.; Heng, H.L.; Ooi, L.; Chung, A.; Chow, P.; Cheow, P.C.; Lee, S.Y.; Choo, S.P.; Tan, I.B.; Duda, D.; Nastase, A.; Myint, S.S.; Wong, B.H.; Gan, A.; Rajasegaran, V.; Ng, C.C.; Nagarajan, S.; Jusakul, A.; Zhang, S.; Vohra, P.; Yu, W.; Huang, D.; Sithithaworn, P.; Yongvanit, P.; Wongkham, S.; Khuntikeo, N.; Bhudhisawasdi, V.; Popescu, I.; Rozen, S.G.; Tan, P.; Teh, B.T. Exome sequencing identifies distinct mutational patterns in liver fluke-related and non-infection-related bile duct cancers. *Nat. Genet.,* **2013**, *45*(12), 1474-1478.

[16] Ong, C.K.; Subimerb, C.; Pairojkul, C.; Wongkham, S.; Cutcutache, I.; Yu, W.; McPherson, J. R.; Allen, G.E.; Ng, C.C.; Wong, B.H.; Myint, S.S.; Rajasegaran, V.; Heng, H.L.; Gan, A.; Zang, Z.J.; Wu, Y.; Wu, J.; Lee, M.H.; Huang, D.; Ong, P.; Chan-on, W.; Cao, Y.; Qian, C.N.; Lim, K.H.; Ooi, A.; Dykema, K.; Furge, K.; Kukongviriyapan, V.; Sripa, B.; Wongkham, C.; Yongvanit, P.; Futreal, P.A.; Bhudhisawasdi, V.; Rozen, S.; Tan, P.; Teh, B.T. Exome sequencing of liver fluke-associated cholangiocarcinoma. *Nat. Genet.,* **2012,** *44*(6), 690-693.

[17] Jiao, Y.; Pawlik, T.M.; Anders, R.A.; Selaru, F.M.; Streppel, M.M.; Lucas, D.J.; Niknafs, N.; Guthrie, V.B.; Maitra, A.; Argani, P.; Of-

ferhaus, G.J.; Roa, J.C.; Roberts, L.R.; Gores, G.J.; Popescu, I.; Alexandrescu, S.T.; Dima, S.; Fassan, M.; Simbolo, M.; Mafficini, A.; Capelli, P.; Lawlor, R.T.; Ruzzenente, A.; Guglielmi, A.; Tortora, G.; de Braud, F.; Scarpa, A.; Jarnagin, W.; Klimstra, D.; Karchin, R.; Velculescu, V.E.; Hruban, R.H.; Vogelstein, B.; Kinzler, K.W.; Papadopoulos, N.; Wood, L.D. Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas. *Nat. Genet.,* **2013**, *45*(12), 1470-1473.

[18] Cancer Genome Atlas Research, N.; Kandoth, C.; Schultz, N.; Cherniack, A.D.; Akbani, R.; Liu, Y.; Shen, H.; Robertson, A.G.; Pashtan, I.; Shen, R.; Benz, C.C.; Yau, C.; Laird, P.W.; Ding, L.; Zhang, W.; Mills, G.B.; Kucherlapati, R.; Mardis, E.R.; Levine, D.A. Integrated genomic characterization of endometrial carcinoma. *Nature,* **2013,** *497*(7447), 67-73.

[19] Seshagiri, S.; Stawiski, E.W.; Durinck, S.; Modrusan, Z.; Storm, E.E.; Conboy, C.B.; Chaudhuri, S.; Guan, Y.; Janakiraman, V.; Jaiswal, B.S.; Guillory, J.; Ha, C.; Dijkgraaf, G.J.; Stinson, J.; Gnad, F.; Huntley, M.A.; Degenhardt, J.D.; Haverty, P.M.; Bourgon, R.; Wang, W.; Koeppen, H.; Gentleman, R.; Starr, T.K.; Zhang, Z.; Largaespada, D.A.; Wu, T.D.; de Sauvage, F.J. Recurrent R-spondin fusions in colon cancer. *Nature,* **2012**, *488*(7413), 660-664.

[20] Cancer Genome Atlas, N. Comprehensive molecular characterization of human colon and rectal cancer. *Nature,* **2012**, *487*(7407), 330-337.

[21] Ahn, S.M.; Jang, S.J.; Shim, J.H.; Kim, D.; Hong, S.M.; Sung, C.O.; Baek, D.; Haq, F.; Ansari, A.A.; Lee, S.Y.; Chun, S.M.; Choi, S.; Choi, H.J.; Kim, J.; Kim, S.; Hwang, S.; Lee, Y.J.; Lee, J.E.; Jung, W.R.; Jang, H.Y.; Yang, E.; Sung, W.K.; Lee, N.P.; Mao, M.; Lee, C.; Zucman-Rossi, J.; Yu, E.; Lee, H.C.; Kong, G. Genomic portrait of resectable hepatocellular carcinomas: implications of RB1 and FGF19 aberrations for patient stratification. *Hepatology,* **2014**, *60*(6), 1972-1982.

[22] Fujimoto, A.; Totoki, Y.; Abe, T.; Boroevich, K.A.; Hosoda, F.; Nguyen, H.H.; Aoki, M.; Hosono, N.; Kubo, M.; Miya, F.; Arai, Y.; Takahashi, H.; Shirakihara, T.; Nagasaki, M.; Shibuya, T.; Nakano, K.; Watanabe-Makino, K.; Tanaka, H.; Nakamura, H.; Kusuda, J.; Ojima, H.; Shimada, K.; Okusaka, T.; Ueno, M.; Shigekawa, Y.; Kawakami, Y.; Arihiro, K.; Ohdan, H.; Gotoh, K.; Ishikawa, O.; Ariizumi, S.; Yamamoto, M.; Yamada, T.; Chayama, K.; Kosuge, T.; Yamaue, H.; Kamatani, N.; Miyano, S.; Nakagama, H.; Nakamura, Y.; Tsunoda, T.; Shibata, T.; Nakagawa, H. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. *Nat. Genet.,* **2012**, *44*(7), 760-764.

[23] Guo, G.; Sun, X.; Chen, C.; Wu, S.; Huang, P.; Li, Z.; Dean, M.; Huang, Y.; Jia, W.; Zhou, Q.; Tang, A.; Yang, Z.; Li, X.; Song, P.; Zhao, X.; Ye, R.; Zhang, S.; Lin, Z.; Qi, M.; Wan, S.; Xie, L.; Fan, F.; Nickerson, M.L.; Zou, X.; Hu, X.; Xing, L.; Lv, Z.; Mei, H.; Gao, S.; Liang, C.; Gao, Z.; Lu, J.; Yu, Y.; Liu, C.; Li, L.; Fang, X.; Jiang, Z.; Yang, J.; Li, C.; Zhao, X.; Chen, J.; Zhang, F.; Lai, Y.; Lin, Z.; Zhou, F.; Chen, H.; Chan, H.C.; Tsang, S.; Theodorescu, D.; Li, Y.; Zhang, X.; Wang, J.; Yang, H.; Gui, Y.; Wang, J.; Cai, Z. Whole-genome and whole-exome sequencing of bladder cancer identifies frequent alterations in genes involved in sister chromatid cohesion and segregation. *Nat. Genet.,* **2013**, *45*(12), 1459-1463.

[24] Kim, P.H.; Cha, E.K.; Sfakianos, J.P.; Iyer, G.; Zabor, E.C.; Scott, S.N.; Ostrovnaya, I.; Ramirez, R.; Sun, A.; Shah, R.; Yee, A.M.; Reuter, V.E.; Bajorin, D.F.; Rosenberg, J.E.; Schultz, N.; Berger, M.F.; Al-Ahmadie, H.A.; Solit, D.B.; Bochner, B.H. Genomic predictors of survival in patients with high-grade urothelial carcinoma of the bladder. *Eur. Urol.,* **2015**, *67*(2), 198-201.

[25] Cancer Genome Atlas Research, N. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature,* **2014**, *507*(7492), 315-322.

[26] Hodis, E.; Watson, I.R.; Kryukov, G.V.; Arold, S.T.; Imielinski, M.; Theurillat, J.P.; Nickerson, E.; Auclair, D.; Li, L.; Place, C.; Dicara, D.; Ramos, A.H.; Lawrence, M.S.; Cibulskis, K.; Sivachenko, A.; Voet, D.; Saksena, G.; Stransky, N.; Onofrio, R.C.; Winckler, W.; Ardlie, K.; Wagle, N.; Wargo, J.; Chong, K.; Morton, D.L.; Stemke-Hale, K.; Chen, G.; Noble, M.; Meyerson, M.; Ladbury, J.E.; Davies, M.A.; Gershenwald, J.E.; Wagner, S.N.; Hoon, D.S.; Schadendorf, D.; Lander, E.S.; Gabriel, S.B.; Getz, G.; Garraway, L.A.; Chin, L. A landscape of driver mutations in melanoma. *Cell,* **2012**, *150*(2), 251-263.

[27] Krauthammer, M.; Kong, Y.; Ha, B.H.; Evans, P.; Bacchiocchi, A.; McCusker, J.P.; Cheng, E.; Davis, M.J.; Goh, G.; Choi, M.; Ariyan, S.; Narayan, D.; Dutton-Regester, K.; Capatana, A.; Holman, E.C.; Bosenberg, M.; Sznol, M.; Kluger, H.M.; Brash, D.E.; Stern, D.F.; Materin, M.A.; Lo, R.S.; Mane, S.; Ma, S.; Kidd, K.K.; Hayward, N.K.; Lifton, R.P.; Schlessinger, J.; Boggon, T. J.; Halaban, R. Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. *Nat. Genet.,* **2012**, *44*(9), 1006-1014.

[28] Berger, M.F.; Hodis, E.; Heffernan, T.P.; Deribe, Y.L.; Lawrence, M.S.; Protopopov, A.; Ivanova, E.; Watson, I.R.; Nickerson, E.; Ghosh, P.; Zhang, H.; Zeid, R.; Ren, X.; Cibulskis, K.; Sivachenko, A.Y.; Wagle, N.; Sucker, A.; Sougnez, C.; Onofrio, R.; Ambrogio, L.; Auclair, D.; Fennell, T.; Carter, S.L.; Drier, Y.; Stojanov, P.; Singer, M.A.; Voet, D.; Jing, R.; Saksena, G.; Barretina, J.; Ramos, A.H.; Pugh, T.J.; Stransky, N.; Parkin, M.; Winckler, W.; Mahan, S.; Ardlie, K.; Baldwin, J.; Wargo, J.; Schadendorf, D.; Meyerson, M.; Gabriel, S.B.; Golub, T.R.; Wagner, S.N.; Lander, E.S.; Getz, G.; Chin, L.; Garraway, L.A. Melanoma genome sequencing reveals frequent PREX2 mutations. *Nature,* **2012**, *485*(7399), 502-506.

[29] Imielinski, M.; Berger, A.H.; Hammerman, P.S.; Hernandez, B.; Pugh, T.J.; Hodis, E.; Cho, J.; Suh, J.; Capelletti, M.; Sivachenko, A.; Sougnez, C.; Auclair, D.; Lawrence, M.S.; Stojanov, P.; Cibulskis, K.; Choi, K.; de Waal, L.; Sharifnia, T.; Brooks, A.; Greulich, H.; Banerji, S.; Zander, T.; Seidel, D.; Leenders, F.; Ansen, S.; Ludwig, C.; Engel-Riedel, W.; Stoelben, E.; Wolf, J.; Goparju, C.; Thompson, K.; Winckler, W.; Kwiatkowski, D.; Johnson, B.E.; Janne, P.A.; Miller, V.A.; Pao, W.; Travis, W.D.; Pass, H.I.; Gabriel, S.B.; Lander, E.S.; Thomas, R.K.; Garraway, L.A.; Getz, G.; Meyerson, M. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell,* **2012**, *150*(6), 1107-1120.

[30] Cancer Genome Atlas Research, N. Comprehensive molecular profiling of lung adenocarcinoma. *Nature,* **2014,** *511*(7511), 543-550.

[31] Rudin, C.M.; Durinck, S.; Stawiski, E.W.; Poirier, J.T.; Modrusan, Z.; Shames, D.S.; Bergbower, E.A.; Guan, Y.; Shin, J.; Guillory, J.; Rivers, C.S.; Foo, C.K.; Bhatt, D.; Stinson, J.; Gnad, F.; Haverty, P.M.; Gentleman, R.; Chaudhuri, S.; Janakiraman, V.; Jaiswal, B.S.; Parikh, C.; Yuan, W.; Zhang, Z.; Koeppen, H.; Wu, T.D.; Stern, H.M.; Yauch, R.L.; Huffman, K.E.; Paskulin, D.D.; Illei, P.B.; Varella-Garcia, M.; Gazdar, A.F.; de Sauvage, F.J.; Bourgon, R.; Minna, J.D.; Brock, M.V.; Seshagiri, S. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. *Nat. Genet.,* **2012**, *44*(10), 1111-1116.

[32] Cancer Genome Atlas Research, N. Comprehensive genomic characterization of squamous cell lung cancers. *Nature,* **2012**, *489*(7417), 519-25.

[33] Biankin, A.V.; Waddell, N.; Kassahn, K.S.; Gingras, M.C.; Muthuswamy, L.B.; Johns, A.L.; Miller, D.K.; Wilson, P.J.; Patch, A.M.; Wu, J.; Chang, D.K.; Cowley, M.J.; Gardiner, B.B.; Song, S.; Harliwong, I.; Idrisoglu, S.; Nourse, C.; Nourbakhsh, E.; Manning, S.; Wani, S.; Gongora, M.; Pajic, M.; Scarlett, C.J.; Gill, A.J.; Pinho, A.V.; Rooman, I.; Anderson, M.; Holmes, O.; Leonard, C.; Taylor, D.; Wood, S.; Xu, Q.; Nones, K.; Fink, J.L.; Christ, A.; Bruxner, T.; Cloonan, N.; Kolle, G.; Newell, F.; Pinese, M.; Mead, R.S.; Humphris, J.L.; Kaplan, W.; Jones, M.D.; Colvin, E.K.; Nagrial, A.M.; Humphrey, E.S.; Chou, A.; Chin, V.T.; Chantrill, L.A.; Mawson, A.; Samra, J.S.; Kench, J.G.; Lovell, J.A.; Daly, R.J.; Merrett, N.D.; Toon, C.; Epari, K.; Nguyen, N.Q.; Barbour, A.; Zeps, N.; Australian Pancreatic Cancer Genome, I.; Kakkar, N.; Zhao, F.; Wu, Y.Q.; Wang, M.; Muzny, D.M.; Fisher, W.E.; Brunicardi, F.C.; Hodges, S.E.; Reid, J.G.; Drummond, J.; Chang, K.; Han, Y.; Lewis, L.R.; Dinh, H.; Buhay, C.J.; Beck, T.; Timms, L.; Sam, M.; Begley, K.; Brown, A.; Pai, D.; Panchal, A.; Buchner, N.; De Borja, R.; Denroche, R.E.; Yung, C.K.; Serra, S.; Onetto, N.; Mukhopadhyay, D.; Tsao, M.S.; Shaw, P.A.; Petersen, G.M.; Gallinger, S.; Hruban, R.H.; Maitra, A.; Iacobuzio-Donahue, C.A.; Schulick, R.D.; Wolfgang, C.L.; Morgan, R.A.; Lawlor, R.T.; Capelli, P.; Corbo, V.; Scardoni, M.; Tortora, G.; Tempero, M.A.; Mann, K.M.; Jenkins, N.A.; Perez-Mancera, P.A.; Adams, D.J.; Largaespada, D.A.; Wessels, L.F.; Rust, A.G.; Stein, L.D.; Tuveson, D.A.; Copeland, N.G.; Musgrove, E.A.; Scarpa, A.; Eshleman, J.R.; Hudson, T.J.; Sutherland, R.L.; Wheeler, D.A.; Pearson, J.V.; McPherson, J.D.; Gibbs, R.A.; Grimmond, S.M. Pancreatic cancer

genomes reveal aberrations in axon guidance pathway genes. *Nature,* **2012**, *491*(7424), 399-405.

[34] Cancer Genome Atlas Research, N. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N. Engl. J. Med.,* **2013,** *368*(22), 2059-2074.

[35] Lohr, J.G.; Stojanov, P.; Carter, S.L.; Cruz-Gordillo, P.; Lawrence, M.S.; Auclair, D.; Sougnez, C.; Knoechel, B.; Gould, J.; Saksena, G.; Cibulskis, K.; McKenna, A.; Chapman, M.A.; Straussman, R.; Levy, J.; Perkins, L.M.; Keats, J.J.; Schumacher, S.E.; Rosenberg, M.; Multiple Myeloma Research, C.; Getz, G.; Golub, T. R. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. *Cancer Cell,* **2014**, *25*(1), 91-101.

[36] Shah, S.P.; Roth, A.; Goya, R.; Oloumi, A.; Ha, G.; Zhao, Y.; Turashvili, G.; Ding, J.; Tse, K.; Haffari, G.; Bashashati, A.; Prentice, L.M.; Khattra, J.; Burleigh, A.; Yap, D.; Bernard, V.; McPherson, A.; Shumansky, K.; Crisan, A.; Giuliany, R.; Heravi-Moussavi, A.; Rosner, J.; Lai, D.; Birol, I.; Varhol, R.; Tam, A.; Dhalla, N.; Zeng, T.; Ma, K.; Chan, S.K.; Griffith, M.; Moradian, A.; Cheng, S.W.; Morin, G.B.; Watson, P.; Gelmon, K.; Chia, S.; Chin, S.F.; Curtis, C.; Rueda, O.M.; Pharoah, P.D.; Damaraju, S.; Mackey, J.; Hoon, K.; Harkins, T.; Tadigotla, V.; Sigaroudinia, M.; Gascard, P.; Tlsty, T.; Costello, J.F.; Meyer, I.M.; Eaves, C.J.; Wasserman, W.W.; Jones, S.; Huntsman, D.; Hirst, M.; Caldas, C.; Marra, M.A.; Aparicio, S. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature,* **2012**, *486*(7403), 395-399.

[37] Banerji, S.; Cibulskis, K.; Rangel-Escareno, C.; Brown, K.K.; Carter, S.L.; Frederick, A.M.; Lawrence, M.S.; Sivachenko, A.Y.; Sougnez, C.; Zou, L.; Cortes, M.L.; Fernandez-Lopez, J.C.; Peng, S.; Ardlie, K.G.; Auclair, D.; Bautista-Pina, V.; Duke, F.; Francis, J.; Jung, J.; Maffuz-Aziz, A.; Onofrio, R.C.; Parkin, M.; Pho, N.H.; Quintanar-Jurado, V.; Ramos, A.H.; Rebollar-Vega, R.; Rodriguez-Cuevas, S.; Romero-Cordoba, S.L.; Schumacher, S.E.; Stransky, N.; Thompson, K.M.; Uribe-Figueroa, L.; Baselga, J.; Beroukhim, R.; Polyak, K.; Sgroi, D.C.; Richardson, A.L.; Jimenez-Sanchez, G.; Lander, E.S.; Gabriel, S.B.; Garraway, L.A.; Golub, T.R.; Melendez-Zajgla, J.; Toker, A.; Getz, G.; Hidalgo-Miranda, A.; Meyerson, M. Sequence analysis of mutations and translocations across breast cancer subtypes. *Nature,* **2012**, *486*(7403), 405-409.

[38] Stephens, P.J.; Tarpey, P.S.; Davies, H.; Van Loo, P.; Greenman, C.; Wedge, D.C.; Nik-Zainal, S.; Martin, S.; Varela, I.; Bignell, G.R.; Yates, L.R.; Papaemmanuil, E.; Beare, D.; Butler, A.; Cheverton, A.; Gamble, J.; Hinton, J.; Jia, M.; Jayakumar, A.; Jones, D.; Latimer, C.; Lau, K.W.; McLaren, S.; McBride, D.J.; Menzies, A.; Mudie, L.; Raine, K.; Rad, R.; Chapman, M.S.; Teague, J.; Easton, D.; Langerod, A.; Oslo Breast Cancer, C.; Lee, M.T.; Shen, C.Y.; Tee, B.T.; Huimin, B.W.; Broeks, A.; Vargas, A.C.; Turashvili, G.; Martens, J.; Fatima, A.; Miron, P.; Chin, S.F.; Thomas, G.; Boyault, S.; Mariani, O.; Lakhani, S.R.; van de Vijver, M.; van 't Veer, L.; Foekens, J.; Desmedt, C.; Sotiriou, C.; Tutt, A.; Caldas, C.; Reis-Filho, J.S.; Aparicio, S.A.; Salomon, A.V.; Borresen-Dale, A.L.; Richardson, A.L.; Campbell, P.J.; Futreal, P.A.; Stratton, M. R. The landscape of cancer genes and mutational processes in breast cancer. *Nature,* **2012**, *486*(7403), 400-404.

[39] Cancer Genome Atlas, N. Comprehensive molecular portraits of human breast tumours. *Nature,* **2012,** *490*(7418), 61-70.

[40] Guo, G.; Gui, Y.; Gao, S.; Tang, A.; Hu, X.; Huang, Y.; Jia, W.; Li, Z.; He, M.; Sun, L.; Song, P.; Sun, X.; Zhao, X.; Yang, S.; Liang, C.; Wan, S.; Zhou, F.; Chen, C.; Zhu, J.; Li, X.; Jian, M.; Zhou, L.; Ye, R.; Huang, P.; Chen, J.; Jiang, T.; Liu, X.; Wang, Y.; Zou, J.; Jiang, Z.; Wu, R.; Wu, S.; Fan, F.; Zhang, Z.; Liu, L.; Yang, R.; Liu, X.; Wu, H.; Yin, W.; Zhao, X.; Liu, Y.; Peng, H.; Jiang, B.; Feng, Q.; Li, C.; Xie, J.; Lu, J.; Kristiansen, K.; Li, Y.; Zhang, X.; Li, S.; Wang, J.; Yang, H.; Cai, Z.; Wang, J. Frequent mutations of genes encoding ubiquitin-mediated proteolysis pathway components in clear cell renal cell carcinoma. *Nat. Genet.,* **2012,** *44*(1), 17-19.

[41] Cancer Genome Atlas Research, N. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature,* **2013,** *499*(7456), 43-49.

[42] Cancer Genome Atlas Research, N. Integrated genomic analyses of ovarian carcinoma. *Nature,* **2011,** *474*(7353), 609-615.

[43] Versteege, I.; Sevenet, N.; Lange, J.; Rousseau-Merck, M.F.; Ambros, P.; Handgretinger, R.; Aurias, A.; Delattre, O. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature,* **1998,** *394*(6689), 203-206.

[44] Dulak, A.M.; Stojanov, P.; Peng, S.; Lawrence, M.S.; Fox, C.; Stewart, C.; Bandla, S.; Imamura, Y.; Schumacher, S.E.; Shefler, E.; McKenna, A.; Carter, S.L.; Cibulskis, K.; Sivachenko, A.; Saksena, G.; Voet, D.; Ramos, A.H.; Auclair, D.; Thompson, K.; Sougnez, C.; Onofrio, R.C.; Guiducci, C.; Beroukhim, R.; Zhou, Z.; Lin, L.; Lin, J.; Reddy, R.; Chang, A.; Landrenau, R.; Pennathur, A.; Ogino, S.; Luketich, J.D.; Golub, T.R.; Gabriel, S.B.; Lander, E.S.; Beer, D.G.; Godfrey, T.E.; Getz, G.; Bass, A.J. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. *Nat. Genet.,* **2013**, *45*(5), 478-486.

[45] Pugh, T.J.; Weeraratne, S.D.; Archer, T.C.; Pomeranz Krummel, D.A.; Auclair, D.; Bochicchio, J.; Carneiro, M.O.; Carter, S.L.; Cibulskis, K.; Erlich, R.L.; Greulich, H.; Lawrence, M.S.; Lennon, N.J.; McKenna, A.; Meldrim, J.; Ramos, A.H.; Ross, M.G.; Russ, C.; Shefler, E.; Sivachenko, A.; Sogoloff, B.; Stojanov, P.; Tamayo, P.; Mesirov, J.P.; Amani, V.; Teider, N.; Sengupta, S.; Francois, J.P.; Northcott, P.A.; Taylor, M.D.; Yu, F.; Crabtree, G.R.; Kautzman, A.G.; Gabriel, S.B.; Getz, G.; Jager, N.; Jones, D.T.; Lichter, P.; Pfister, S.M.; Roberts, T.M.; Meyerson, M.; Pomeroy, S.L.; Cho, Y.J. Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. *Nature,* **2012,** *488*(7409), 106-110.

[46] Jones, D.T.; Jager, N.; Kool, M.; Zichner, T.; Hutter, B.; Sultan, M.; Cho, Y.J.; Pugh, T.J.; Hovestadt, V.; Stutz, A.M.; Rausch, T.; Warnatz, H.J.; Ryzhova, M.; Bender, S.; Sturm, D.; Pleier, S.; Cin, H.; Pfaff, E.; Sieber, L.; Wittmann, A.; Remke, M.; Witt, H.; Hutter, S.; Tzaridis, T.; Weischenfeldt, J.; Raeder, B.; Avci, M.; Amstislavskiy, V.; Zapatka, M.; Weber, U.D.; Wang, Q.; Lasitschka, B.; Bartholomae, C.C.; Schmidt, M.; von Kalle, C.; Ast, V.; Lawerenz, C.; Eils, J.; Kabbe, R.; Benes, V.; van Sluis, P.; Koster, J.; Volckmann, R.; Shih, D.; Betts, M.J.; Russell, R.B.; Coco, S.; Tonini, G.P.; Schuller, U.; Hans, V.; Graf, N.; Kim, Y.J.; Monoranu, C.; Roggendorf, W.; Unterberg, A.; Herold-Mende, C.; Milde, T.; Kulozik, A.E.; von Deimling, A.; Witt, O.; Maass, E.; Rossler, J.; Ebinger, M.; Schuhmann, M.U.; Fruhwald, M.C.; Hasselblatt, M.; Jabado, N.; Rutkowski, S.; von Bueren, A.O.; Williamson, D.; Clifford, S.C.; McCabe, M.G.; Collins, V.P.; Wolf, S.; Wiemann, S.; Lehrach, H.; Brors, B.; Scheurlen, W.; Felsberg, J.; Reifenberger, G.; Northcott, P.A.; Taylor, M.D.; Meyerson, M.; Pomeroy, S.L.; Yaspo, M.L.; Korbel, J.O.; Korshunov, A.; Eils, R.; Pfister, S.M.; Lichter, P. Dissecting the genomic complexity underlying medulloblastoma. *Nature,* **2012,** *488*(7409), 100-105.

[47] Robinson, G.; Parker, M.; Kranenburg, T.A.; Lu, C.; Chen, X.; Ding, L.; Phoenix, T.N.; Hedlund, E.; Wei, L.; Zhu, X.; Chalhoub, N.; Baker, S.J.; Huether, R.; Kriwacki, R.; Curley, N.; Thiruvenkatam, R.; Wang, J.; Wu, G.; Rusch, M.; Hong, X.; Becksfort, J.; Gupta, P.; Ma, J.; Easton, J.; Vadodaria, B.; Onar-Thomas, A.; Lin, T.; Li, S.; Pounds, S.; Paugh, S.; Zhao, D.; Kawauchi, D.; Roussel, M.F.; Finkelstein, D.; Ellison, D.W.; Lau, C.C.; Bouffet, E.; Hassall, T.; Gururangan, S.; Cohn, R.; Fulton, R. S.; Fulton, L.L.; Dooling, D.J.; Ochoa, K.; Gajjar, A.; Mardis, E.R.; Wilson, R.K.; Downing, J.R.; Zhang, J.; Gilbertson, R.J. Novel mutations target distinct subgroups of medulloblastoma. *Nature,* **2012,** *488*(7409), 43-48.

[48] Ho, A.S.; Kannan, K.; Roy, D.M.; Morris, L.G.; Ganly, I.; Katabi, N.; Ramaswami, D.; Walsh, L.A.; Eng, S.; Huse, J.T.; Zhang, J.; Dolgalev, I.; Huberman, K.; Heguy, A.; Viale, A.; Drobnjak, M.; Leversha, M.A.; Rice, C.E.; Singh, B.; Iyer, N.G.; Leemans, C.R.; Bloemena, E.; Ferris, R.L.; Seethala, R.R.; Gross, B.E.; Liang, Y.; Sinha, R.; Peng, L.; Raphael, B.J.; Turcan, S.; Gong, Y.; Schultz, N.; Kim, S.; Chiosea, S.; Shah, J.P.; Sander, C.; Lee, W.; Chan, T.A. The mutational landscape of adenoid cystic carcinoma. *Nat. Genet.,* **2013,** *45*(7), 791-798.

[49] Peifer, M.; Fernandez-Cuesta, L.; Sos, M.L.; George, J.; Seidel, D.; Kasper, L.H.; Plenker, D.; Leenders, F.; Sun, R.; Zander, T.; Menon, R.; Koker, M.; Dahmen, I.; Muller, C.; Di Cerbo, V.; Schildhaus, H.U.; Altmuller, J.; Baessmann, I.; Becker, C.; de Wilde, B.; Vandesompele, J.; Bohm, D.; Ansen, S.; Gabler, F.; Wilkening, I.; Heynck, S.; Heuckmann, J.M.; Lu, X.; Carter, S.L.; Cibulskis, K.; Banerji, S.; Getz, G.; Park, K.S.; Rauh, D.; Grutter, C.; Fischer, M.; Pasqualucci, L.; Wright, G.; Wainer, Z.; Russell, P.; Petersen, I.; Chen, Y.; Stoelben, E.; Ludwig, C.; Schnabel, P.; Hoffmann, H.; Muley, T.; Brockmann, M.; Engel-Riedel, W.; Muscarella, L.A.; Fazio, V.M.; Groen, H.; Timens, W.; Sietsma, H.; Thunnissen, E.; Smit, E.; Heideman, D.A.; Snijders, P.J.; Cappuzzo, F.; Ligorio, C.;

Damiani, S.; Field, J.; Solberg, S.; Brustugun, O.T.; Lund-Iversen, M.; Sanger, J.; Clement, J.H.; Soltermann, A.; Moch, H.; Weder, W.; Solomon, B.; Soria, J.C.; Validire, P.; Besse, B.; Brambilla, E.; Brambilla, C.; Lantuejoul, S.; Lorimier, P.; Schneider, P.M.; Hallek, M.; Pao, W.; Meyerson, M.; Sage, J.; Shendure, J.; Schneider, R.; Buttner, R.; Wolf, J.; Nurnberg, P.; Perner, S.; Heukamp, L.C.; Brindle, P.K.; Haas, S.; Thomas, R.K. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat. Genet.,* **2012,** *44*(10), 1104-1110.

[50] Glaros, S.; Cirrincione, G.M.; Muchardt, C.; Kleer, C.G.; Michael, C.W.; Reisman, D. The reversible epigenetic silencing of BRM: implications for clinical targeted therapy. *Oncogene,* **2007,** *26*(49), 7058-7066.

[51] Fukuoka, J.; Fujii, T.; Shih, J.H.; Dracheva, T.; Meerzaman, D.; Player, A.; Hong, K.; Settnek, S.; Gupta, A.; Buetow, K.; Hewitt, S.; Travis, W.D.; Jen, J. Chromatin remodeling factors and BRM/BRG1 expression as prognostic indicators in non-small cell lung cancer. *Clin. Cancer Res.,* **2004,** *10*(13), 4314-4324.

[52] Reisman, D.N.; Sciarrotta, J.; Wang, W.; Funkhouser, W.K.; Weissman, B.E. Loss of BRG1/BRM in human lung cancer cell lines and primary lung cancers: correlation with poor prognosis. *Cancer Res.,* **2003,** *63*(3), 560-566.

[53] Brizuela, B.J.; Elfring, L.; Ballard, J.; Tamkun, J.W.; Kennison, J.A. Genetic analysis of the brahma gene of Drosophila melanogaster and polytene chromosome subdivisions 72AB. *Genetics,* **1994,** *137*(3), 803-813.

[54] Elfring, L.K.; Deuring, R.; McCallum, C.M.; Peterson, C.L.; Tamkun, J.W. Identification and characterization of Drosophila relatives of the yeast transcriptional activator SNF2/SWI2. *Mol. Cell Biol.,* **1994,** *14*(4), 2225-2234.

[55] Okabe, I.; Bailey, L.C.; Attree, O.; Srinivasan, S.; Perkel, J.M.; Laurent, B.C.; Carlson, M.; Nelson, D.L.; Nussbaum, R.L. Cloning of human and bovine homologs of SNF2/SWI2: a global activator of transcription in yeast S. cerevisiae. *Nucleic Acids Res.,* **1992,** *20*(17), 4649-4655.

[56] Tsukiyama, T.; Wu, C. Purification and properties of an ATP-dependent nucleosome remodeling factor. *Cell,* **1995,** *83*(6), 1011-1020.

[57] Aihara, T.; Miyoshi, Y.; Koyama, K.; Suzuki, M.; Takahashi, E.; Monden, M.; Nakamura, Y. Cloning and mapping of SMARCA5 encoding hSNF2H, a novel human homologue of Drosophila ISWI. *Cytogenet. Cell Genet.,* **1998,** *81*(3-4), 191-193.

[58] Tsukiyama, T.; Palmer, J.; Landel, C.C.; Shiloach, J.; Wu, C. Characterization of the imitation switch subfamily of ATP-dependent chromatin-remodeling factors in Saccharomyces cerevisiae. *Genes. Dev.,* **1999,** *13*(6), 686-697.

[59] Corona, D.F.; Tamkun, J.W. Multiple roles for ISWI in transcription, chromosome organization and DNA replication. *Biochim. Biophys. Acta,* **2004,** *1677*(1-3), 113-119.

[60] Yadon, A.N.; Tsukiyama, T. SnapShot: Chromatin remodeling: ISWI. *Cell,* **2011,** *144*(3), 453-453 e1.

[61] Loyola, A.; LeRoy, G.; Wang, Y.H.; Reinberg, D. Reconstitution of recombinant chromatin establishes a requirement for histone-tail modifications during chromatin assembly and transcription. *Genes. Dev.,* **2001,** *15*(21), 2837-2851.

[62] Perpelescu, M.; Nozaki, N.; Obuse, C.; Yang, H.; Yoda, K. Active establishment of centromeric CENP-A chromatin by RSF complex. *J. Cell Biol.,* **2009,** *185*(3), 397-407.

[63] Grasso, C.S.; Wu, Y.M.; Robinson, D.R.; Cao, X.; Dhanasekaran, S.M.; Khan, A.P.; Quist, M.J.; Jing, X.; Lonigro, R.J.; Brenner, J.C.; Asangani, I.A.; Ateeq, B.; Chun, S.Y.; Siddiqui, J.; Sam, L.; Anstett, M.; Mehra, R.; Prensner, J.R.; Palanisamy, N.; Ryslik, G.A.; Vandin, F.; Raphael, B.J.; Kunju, L.P.; Rhodes, D.R.; Pienta, K.J.; Chinnaiyan, A.M.; Tomlins, S.A. The mutational landscape of lethal castration-resistant prostate cancer. *Nature,* **2012,** *487*(7406), 239-243.

[64] Delmas, V.; Stokes, D.G.; Perry, R.P. A mammalian DNA-binding protein that contains a chromodomain and an SNF2/SWI2-like helicase domain. *Proc. Natl. Acad. Sci. U. S. A.,* **1993,** *90*(6), 2414-2418.

[65] Woodage, T.; Basrai, M.A.; Baxevanis, A.D.; Hieter, P.; Collins, F.S. Characterization of the CHD family of proteins. *Proc. Natl. Acad. Sci. U. S. A.,* **1997,** *94*(21), 11472-11477.

[66] Stanley, F.K.; Moore, S.; Goodarzi, A.A. CHD chromatin remodelling enzymes and the DNA damage response. *Mutat. Res.,* **2013,** *750*(1-2), 31-44.

[67] Huang, S.; Gulzar, Z.G.; Salari, K.; Lapointe, J.; Brooks, J.D.; Pollack, J.R. Recurrent deletion of CHD1 in prostate cancer with relevance to cell invasiveness. *Oncogene,* **2012,** *31*(37), 4164-4170.

[68] Liu, W.; Lindberg, J.; Sui, G.; Luo, J.; Egevad, L.; Li, T.; Xie, C.; Wan, M.; Kim, S.T.; Wang, Z.; Turner, A.R.; Zhang, Z.; Feng, J.; Yan, Y.; Sun, J.; Bova, G.S.; Ewing, C.M.; Yan, G.; Gielzak, M.; Cramer, S.D.; Vessella, R.L.; Zheng, S.L.; Grönberg, H.; Isaacs, W.B.; Xu, J. Identification of novel CHD1-associated collaborative alterations of genomic structure and functional assessment of CHD1 in prostate cancer. *Oncogene,* **2012,** *31*(35), 3939-3948.

[69] Nagarajan, P.; Onami, T.M.; Rajagopalan, S.; Kania, S.; Donnell, R.; Venkatachalam, S. Role of chromodomain helicase DNA-binding protein 2 in DNA damage response signaling and tumorigenesis. *Oncogene,* **2009,** *28*(8), 1053-1062.

[70] Brunton, H.; Goodarzi, A.A.; Noon, A.T.; Shrikhande, A.; Hansen, R.S.; Jeggo, P.A.; Shibata, A. Analysis of human syndromes with disordered chromatin reveals the impact of heterochromatin on the efficacy of ATM-dependent G2/M checkpoint arrest. *Mol. Cell Biol.,* **2011,** *31*(19), 4022-4035.

[71] Barbieri, C.E.; Baca, S.C.; Lawrence, M.S.; Demichelis, F.; Blattner, M.; Theurillat, J.P.; White, T.A.; Stojanov, P.; Van Allen, E.; Stransky, N.; Nickerson, E.; Chae, S.S.; Boysen, G.; Auclair, D.; Onofrio, R.C.; Park, K.; Kitabayashi, N.; MacDonald, T.Y.; Sheikh, K.; Vuong, T.; Guiducci, C.; Cibulskis, K.; Sivachenko, A.; Carter, S.L.; Saksena, G.; Voet, D.; Hussain, W.M.; Ramos, A.H.; Winckler, W.; Redman, M.C.; Ardlie, K.; Tewari, A.K.; Mosquera, J.M.; Rupp, N.; Wild, P.J.; Moch, H.; Morrissey, C.; Nelson, P.S.; Kantoff, P.W.; Gabriel, S.B.; Golub, T.R.; Meyerson, M.; Lander, E.S.; Getz, G.; Rubin, M.A.; Garraway, L.A. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. *Nat. Genet.,* **2012,** *44*(6), 685-689.

[72] Zhao, S.; Choi, M.; Overton, J.D.; Bellone, S.; Roque, D.M.; Cocco, E.; Guzzo, F.; English, D.P.; Varughese, J.; Gasparrini, S.; Bortolomai, I.; Buza, N.; Hui, P.; Abu-Khalaf, M.; Ravaggi, A.; Bignotti, E.; Bandiera, E.; Romani, C.; Todeschini, P.; Tassi, R.; Zanotti, L.; Carrara, L.; Pecorelli, S.; Silasi, D.-A.; Ratner, E.; Azodi, M.; Schwartz, P.E.; Rutherford, T.J.; Stiegler, A.L.; Mane, S.; Boggon, T.J.; Schlessinger, J.; Lifton, R.P.; Santin, A.D. Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma. *Proc. Natl. Acad. Sci. U. S. A.,* **2013,** *110*(8), 2916-2921.

[73] Le Gallo, M.; O'Hara, A.J.; Rudd, M.L.; Urick, M.E.; Hansen, N.F.; O'Neil, N.J.; Price, J.C.; Zhang, S.; England, B.M.; Godwin, A.K.; Sgroi, D.C.; Program, N.C.S.; Hieter, P.; Mullikin, J.C.; Merino, M.J.; Bell, D.W. Exome sequencing of serous endometrial tumors identifies recurrent somatic mutations in chromatin-remodeling and ubiquitin ligase complex genes. *Nat. Genet.,* **2012,** *44*(12), 1310-1315.

[74] Polo, S.E.; Kaidi, A.; Baskcomb, L.; Galanty, Y.; Jackson, S.P. Regulation of DNA-damage responses and cell-cycle progression by the chromatin remodelling factor CHD4. *EMBO J.,* **2010,** *29*(18), 3130-3139.

[75] Stransky, N.; Egloff, A.M.; Tward, A.D.; Kostic, A.D.; Cibulskis, K.; Sivachenko, A.; Kryukov, G.V.; Lawrence, M.S.; Sougnez, C.; McKenna, A.; Shefler, E.; Ramos, A.H.; Stojanov, P.; Carter, S.L.; Voet, D.; Cortes, M.L.; Auclair, D.; Berger, M.F.; Saksena, G.; Guiducci, C.; Onofrio, R.C.; Parkin, M.; Romkes, M.; Weissfeld, J.L.; Seethala, R.R.; Wang, L.; Rangel-Escareno, C.; Fernandez-Lopez, J.C.; Hidalgo-Miranda, A.; Melendez-Zajgla, J.; Winckler, W.; Ardlie, K.; Gabriel, S.B.; Meyerson, M.; Lander, E.S.; Getz, G.; Golub, T.R.; Garraway, L.A.; Grandis, J.R. The mutational landscape of head and neck squamous cell carcinoma. *Science,* **2011,** *333*(6046), 1157-1160.

[76] Gui, Y.; Guo, G.; Huang, Y.; Hu, X.; Tang, A.; Gao, S.; Wu, R.; Chen, C.; Li, X.; Zhou, L.; He, M.; Li, Z.; Sun, X.; Jia, W.; Chen, J.; Yang, S.; Zhou, F.; Zhao, X.; Wan, S.; Ye, R.; Liang, C.; Liu, Z.; Huang, P.; Liu, C.; Jiang, H.; Wang, Y.; Zheng, H.; Sun, L.; Liu, X.; Jiang, Z.; Feng, D.; Chen, J.; Wu, S.; Zou, J.; Zhang, Z.; Yang, R.; Zhao, J.; Xu, C.; Yin, W.; Guan, Z.; Ye, J.; Zhang, H.; Li, J.; Kristiansen, K.; Nickerson, M.L.; Theodorescu, D.; Li, Y.; Zhang, X.; Li, S.; Wang, J.; Yang, H.; Wang, J.; Cai, Z. Frequent mutations of chromatin remodeling genes in transitional cell carcinoma of the bladder. *Nat. Genet.,* **2011,** *43*(9), 875-878.

[77] Mouradov, D.; Sloggett, C.; Jorissen, R.N.; Love, C.G.; Li, S.; Burgess, A.W.; Arango, D.; Strausberg, R.L.; Buchanan, D.; Wormald, S.; O'Connor, L.; Wilding, J.L.; Bicknell, D.; Tomlinson,

I.P.M.; Bodmer, W.F.; Mariadason, J.M.; Sieber, O.M. Colorectal Cancer Cell Lines Are Representative Models of the Main Molecular Subtypes of Primary Cancer. *Cancer Res.,* **2014,** *74*(12), 3238-3247.

[78] Pleasance, E.D.; Stephens, P.J.; O'Meara, S.; McBride, D.J.; Meynert, A.; Jones, D.; Lin, M.-L.; Beare, D.; Lau, K.W.; Greenman, C.; Varela, I.; Nik-Zainal, S.; Davies, H.R.; Ordoñez, G.R.; Mudie, L.J.; Latimer, C.; Edkins, S.; Stebbings, L.; Chen, L.; Jia, M.; Leroy, C.; Marshall, J.; Menzies, A.; Butler, A.; Teague, J.W.; Mangion, J.; Sun, Y.A.; McLaughlin, S.F.; Peckham, H.E.; Tsung, E.F.; Costa, G.L.; Lee, C.C.; Minna, J.D.; Gazdar, A.; Birney, E.; Rhodes, M.D.; McKernan, K.J.; Stratton, M.R.; Futreal, P.A.; Campbell, P.J. A small cell lung cancer genome reports complex tobacco exposure signatures. *Nature,* **2010,** *463*(7278), 184-190.

[79] Colbert, L.E.; Petrova, A.V.; Fisher, S.B.; Pantazides, B.G.; Madden, M.Z.; Hardy, C.W.; Warren, M.D.; Pan, Y.; Nagaraju, G.P.; Liu, E.A.; Saka, B.; Hall, W.A.; Shelton, J.W.; Gandhi, K.; Pauly, R.; Kowalski, J.; Kooby, D.A.; El-Rayes, B.F.; Staley, C.A.; Adsay, N.V.; Curran, W.J.; Landry, J.C.; Maithel, S.K.; Yu, D.S. CHD7 Expression Predicts Survival Outcomes in Patients with Resected Pancreatic Cancer. *Cancer Res.,* **2014,** *74*(10), 2677-2687.

[80] Damaschke, N.A.; Yang, B.; Blute, M.L.; Lin, C.P.; Huang, W.; Jarrard, D.F. Frequent Disruption of Chromodomain Helicase DNA-Binding Protein 8 (CHD8) and Functionally Associated Chromatin Regulators in Prostate Cancer. *Neoplasia (New York, N.Y.),* **2014,** *16*(12), 1018-1027.

[81] Bao, Y.; Shen, X. INO80 subfamily of chromatin remodeling complexes. *Mutat. Res.,* **2007,** *618*(1-2), 18-29.

[82] Ebbert, R.; Birkmann, A.; Schuller, H.J. The product of the SNF2/SWI2 paralogue INO80 of Saccharomyces cerevisiae required for efficient expression of various yeast structural genes is part of a high-molecular-weight protein complex. *Mol. Microbiol.,* **1999,** *32*(4), 741-751.

[83] Shen, X.; Mizuguchi, G.; Hamiche, A.; Wu, C. A chromatin remodelling complex involved in transcription and DNA processing. *Nature,* **2000,** *406*(6795), 541-544.

[84] van Attikum, H.; Fritsch, O.; Gasser, S.M. Distinct roles for SWR1 and INO80 chromatin remodeling complexes at chromosomal double-strand breaks. *EMBO J.,* **2007,** *26*(18), 4113-4125.

[85] Lu, P.Y.; Levesque, N.; Kobor, M.S. NuA4 and SWR1-C: two chromatin-modifying complexes with overlapping functions and components. *Biochem. Cell Biol.,* **2009,** *87*(5), 799-815.

[86] Lin, D.C.; Meng, X.; Hazawa, M.; Nagata, Y.; Varela, A.M.; Xu, L.; Sato, Y.; Liu, L.Z.; Ding, L.W.; Sharma, A.; Goh, B.C.; Lee, S.C.; Petersson, B.F.; Yu, F.G.; Macary, P.; Oo, M.Z.; Ha, C.S.; Yang, H.; Ogawa, S.; Loh, K.S.; Koeffler, H.P. The genomic landscape of nasopharyngeal carcinoma. *Nat. Genet.,* **2014,** *46*(8), 866-871.

[87] Sykes, S.M.; Mellert, H.S.; Holbert, M.A.; Li, K.; Marmorstein, R.; Lane, W.S.; McMahon, S.B. Acetylation of the p53 DNA-binding domain regulates apoptosis induction. *Mol. Cell,* **2006,** *24*(6), 841-851.

[88] Van Den Broeck, A.; Nissou, D.; Brambilla, E.; Eymin, B.; Gazzeri, S. Activation of a Tip60/E2F1/ERCC1 network in human lung adenocarcinoma cells exposed to cisplatin. *Carcinogenesis,* **2012,** *33*(2), 320-325.

[89] Tang, Y.; Luo, J.; Zhang, W.; Gu, W. Tip60-dependent acetylation of p53 modulates the decision between cell-cycle arrest and apoptosis. *Mol. Cell,* **2006,** *24*(6), 827-839.

[90] Chen, G.; Cheng, Y.; Tang, Y.; Martinka, M.; Li, G. Role of Tip60 in human melanoma cell migration, metastasis, and patient survival. *J. Invest. Dermatol.,* **2012,** *132*(11), 2632-2641.

[91] Ionov, Y.; Matsui, S.; Cowell, J.K. A role for p300/CREB binding protein genes in promoting cancer progression in colon cancer cell lines with microsatellite instability. *Proc. Natl. Acad. Sci. U. S. A.,* **2004,** *101*(5), 1273-1278.

[92] Kishimoto, M.; Kohno, T.; Okudela, K.; Otsuka, A.; Sasaki, H.; Tanabe, C.; Sakiyama, T.; Hirama, C.; Kitabayashi, I.; Minna, J.D.; Takenoshita, S.; Yokota, J. Mutations and deletions of the CBP gene in human lung cancer. *Clin. Cancer Res.,* **2005,** *11*(2 Pt 1), 512-519.

[93] Ianculescu, I.; Wu, D.Y.; Siegmund, K.D.; Stallcup, M.R. Selective roles for cAMP response element-binding protein binding protein and p300 protein as coregulators for androgen-regulated gene expression in advanced prostate cancer cells. *J. Biol. Chem.,* **2012,** *287*(6), 4000-4013.

[94] Santer, F.R.; Hoschele, P.P.; Oh, S.J.; Erb, H.H.; Bouchal, J.; Cavarretta, I.T.; Parson, W.; Meyers, D.J.; Cole, P.A.; Culig, Z. Inhibition of the acetyltransferases p300 and CBP reveals a targetable function for p300 in the survival and invasion pathways of prostate cancer cell lines. *Mol. Cancer Ther.,* **2011,** *10*(9), 1644-1655.

[95] Goto, N.K.; Zor, T.; Martinez-Yamout, M.; Dyson, H.J.; Wright, P.E. Cooperativity in transcription factor binding to the coactivator CREB-binding protein (CBP). The mixed lineage leukemia protein (MLL) activation domain binds to an allosteric site on the KIX domain. *J. Biol. Chem.,* **2002,** *277*(45), 43168-43174.

[96] Rowley, J.D.; Reshmi, S.; Sobulo, O.; Musvee, T.; Anastasi, J.; Raimondi, S.; Schneider, N.R.; Barredo, J.C.; Cantu, E.S.; Schlegelberger, B.; Behm, F.; Doggett, N.A.; Borrow, J.; Zeleznik-Le, N. All patients with the T(11;16)(q23;p13.3) that involves MLL and CBP have treatment-related hematologic disorders. *Blood,* **1997,** *90*(2), 535-541.

[97] Bhaskara, S.; Knutson, S.K.; Jiang, G.; Chandrasekharan, M.B.; Wilson, A.J.; Zheng, S.; Yenamandra, A.; Locke, K.; Yuan, J.L.; Bonine-Summers, A.R.; Wells, C.E.; Kaiser, J.F.; Washington, M.K.; Zhao, Z.; Wagner, F.F.; Sun, Z.W.; Xia, F.; Holson, E.B.; Khabele, D.; Hiebert, S.W. Hdac3 is essential for the maintenance of chromatin structure and genome stability. *Cancer Cell,* **2010,** *18*(5), 436-447.

[98] Heideman, M.R.; Wilting, R.H.; Yanover, E.; Velds, A.; de Jong, J.; Kerkhoven, R.M.; Jacobs, H.; Wessels, L.F.; Dannenberg, J.H. Dosage-dependent tumor suppression by histone deacetylases 1 and 2 through regulation of c-Myc collaborating genes and p53 function. *Blood,* **2013,** *121*(11), 2038-2050.

[99] Licht, J.D. AML1 and the AML1-ETO fusion protein in the pathogenesis of t(8;21) AML. *Oncogene,* **2001,** *20*(40), 5660-5679.

[100] Liu, Y.; Cheney, M.D.; Gaudet, J.J.; Chruszcz, M.; Lukasik, S.M.; Sugiyama, D.; Lary, J.; Cole, J.; Dauter, Z.; Minor, W.; Speck, N.A.; Bushweller, J.H. The tetramer structure of the Nervy homology two domain, NHR2, is critical for AML1/ETO's activity. *Cancer Cell,* **2006,** *9*(4), 249-260.

[101] Rego, E.M.; He, L.Z.; Warrell, R.P., Jr.; Wang, Z.G.; Pandolfi, P.P. Retinoic acid (RA) and As2O3 treatment in transgenic models of acute promyelocytic leukemia (APL) unravel the distinct nature of the leukemogenic process induced by the PML-RARalpha and PLZF-RARalpha oncoproteins. *Proc. Natl. Acad. Sci. U. S. A.,* **2000,** *97*(18), 10173-10178.

[102] Falkenberg, K.J.; Johnstone, R.W. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. *Nat. Rev. Drug Discov.,* **2014,** *13*(9), 673-691.

[103] Morin, R.D.; Mendez-Lago, M.; Mungall, A.J.; Goya, R.; Mungall, K.L.; Corbett, R.D.; Johnson, N.A.; Severson, T.M.; Chiu, R.; Field, M.; Jackman, S.; Krzywinski, M.; Scott, D.W.; Trinh, D.L.; Tamura-Wells, J.; Li, S.; Firme, M.R.; Rogic, S.; Griffith, M.; Chan, S.; Yakovenko, O.; Meyer, I.M.; Zhao, E. Y.; Smailus, D.; Moksa, M.; Chittaranjan, S.; Rimsza, L.; Brooks-Wilson, A.; Spinelli, J.J.; Ben-Neriah, S.; Meissner, B.; Woolcock, B.; Boyle, M.; McDonald, H.; Tam, A.; Zhao, Y.; Delaney, A.; Zeng, T.; Tse, K.; Butterfield, Y.; Birol, I.; Holt, R.; Schein, J.; Horsman, D.E.; Moore, R.; Jones, S.J.; Connors, J.M.; Hirst, M.; Gascoyne, R.D.; Marra, M.A. Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. *Nature,* **2011,** *476*(7360), 298-303.

[104] Morin, R.D.; Johnson, N.A.; Severson, T.M.; Mungall, A.J.; An, J.; Goya, R.; Paul, J.E.; Boyle, M.; Woolcock, B.W.; Kuchenbauer, F.; Yap, D.; Humphries, R.K.; Griffith, O.L.; Shah, S.; Zhu, H.; Kimbara, M.; Shashkin, P.; Charlot, J.F.; Tcherpakov, M.; Corbett, R.; Tam, A.; Varhol, R.; Smailus, D.; Moksa, M.; Zhao, Y.; Delaney, A.; Qian, H.; Birol, I.; Schein, J.; Moore, R.; Holt, R.; Horsman, D.E.; Connors, J.M.; Jones, S.; Aparicio, S.; Hirst, M.; Gascoyne, R.D.; Marra, M.A. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat. Genet.,* **2010,** *42*(2), 181-185.

[105] Wilson, B.G.; Wang, X.; Shen, X.; McKenna, E.S.; Lemieux, M.E.; Cho, Y.J.; Koellhoffer, E.C.; Pomeroy, S.L.; Orkin, S.H.; Roberts, C.W. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell,* **2010,** *18*(4), 316-328.

[106] Chen, M.W.; Hua, K.T.; Kao, H.J.; Chi, C.C.; Wei, L.H.; Johansson, G.; Shiah, S.G.; Chen, P.S.; Jeng, Y.M.; Cheng, T.Y.; Lai, T.C.; Chang, J.S.; Jan, Y.H.; Chien, M.H.; Yang, C.J.; Huang, M.S.; Hsiao, M.; Kuo, M.L. H3K9 histone methyltransferase G9a promotes lung cancer invasion and metastasis by silencing the cell

adhesion molecule Ep-CAM. *Cancer Res.,* **2010,** *70*(20), 7830-7840.

[107] Cho, H.S.; Kelly, J.D.; Hayami, S.; Toyokawa, G.; Takawa, M.; Yoshimatsu, M.; Tsunoda, T.; Field, H.I.; Neal, D.E.; Ponder, B.A.; Nakamura, Y.; Hamamoto, R. Enhanced expression of EHMT2 is involved in the proliferation of cancer cells through negative regulation of SIAH1. *Neoplasia,* **2011,** *13*(8), 676-684.

[108] Dong, C.; Wu, Y.; Yao, J.; Wang, Y.; Yu, Y.; Rychahou, P.G.; Evers, B.M.; Zhou, B.P. G9a interacts with Snail and is critical for Snail-mediated E-cadherin repression in human breast cancer. *J. Clin. Invest.,* **2012,** *122*(4), 1469-1486.

[109] Mohan, M.; Herz, H.M.; Takahashi, Y.H.; Lin, C.; Lai, K.C.; Zhang, Y.; Washburn, M.P.; Florens, L.; Shilatifard, A. Linking H3K79 trimethylation to Wnt signaling through a novel Dot1-containing complex (DotCom). *Genes. Dev.,* **2010,** *24*(6), 574-589.

[110] Mahmoudi, T.; Boj, S.F.; Hatzis, P.; Li, V.S.; Taouatas, N.; Vries, R.G.; Teunissen, H.; Begthel, H.; Korving, J.; Mohammed, S.; Heck, A.J.; Clevers, H. The leukemia-associated Mllt10/Af10-Dot1l are Tcf4/beta-catenin coactivators essential for intestinal homeostasis. *PLoS Biol.,* **2010,** *8*(11), e1000539.

[111] Wang, G.G.; Cai, L.; Pasillas, M.P.; Kamps, M.P. NUP98-NSD1 links H3K36 methylation to Hox-A gene activation and leukaemogenesis. *Nat. Cell Biol.,* **2007,** *9*(7), 804-812.

[112] Toyokawa, G.; Cho, H.S.; Masuda, K.; Yamane, Y.; Yoshimatsu, M.; Hayami, S.; Takawa, M.; Iwai, Y.; Daigo, Y.; Tsuchiya, E.; Tsunoda, T.; Field, H.I.; Kelly, J.D.; Neal, D.E.; Maehara, Y.; Ponder, B.A.; Nakamura, Y.; Hamamoto, R. Histone lysine methyltransferase Wolf-Hirschhorn syndrome candidate 1 is involved in human carcinogenesis through regulation of the Wnt pathway. *Neoplasia,* **2011,** *13*(10), 887-898.

[113] Yang, Y.; Bedford, M.T. Protein arginine methyltransferases and cancer. *Nat. Rev. Cancer,* **2013,** *13*(1), 37-50.

[114] Tzatsos, A.; Paskaleva, P.; Ferrari, F.; Deshpande, V.; Stoykova, S.; Contino, G.; Wong, K.K.; Lan, F.; Trojer, P.; Park, P.J.; Bardeesy, N. KDM2B promotes pancreatic cancer via Polycomb-dependent and -independent transcriptional programs. *J. Clin. Invest.,* **2013,** *123*(2), 727-739.

[115] He, J.; Nguyen, A.T.; Zhang, Y. KDM2b/JHDM1b, an H3K36me2-specific demethylase, is required for initiation and maintenance of acute myeloid leukemia. *Blood,* **2011,** *117*(14), 3869-3880.

[116] Cloos, P.A.; Christensen, J.; Agger, K.; Maiolica, A.; Rappsilber, J.; Antal, T.; Hansen, K.H.; Helin, K. The putative oncogene GASC1 demethylates tri- and dimethylated lysine 9 on histone H3. *Nature,* **2006,** *442*(7100), 307-311.

[117] Patani, N.; Jiang, W.G.; Newbold, R.F.; Mokbel, K. Histone-modifier gene expression profiles are associated with pathological and clinical outcomes in human breast cancer. *Anticancer Res.,* **2011,** *31*(12), 4115-4125.

[118] Shin, S.; Janknecht, R. Activation of androgen receptor by histone demethylases JMJD2A and JMJD2D. *Biochem. Biophys. Res. Commun.,* **2007,** *359*(3), 742-746.

[119] Berry, W.L.; Shin, S.; Lightfoot, S.A.; Janknecht, R. Oncogenic features of the JMJD2A histone demethylase in breast cancer. *Int. J. Oncol.,* **2012,** *41*(5), 1701-1706.

[120] Yamane, K.; Tateishi, K.; Klose, R.J.; Fang, J.; Fabrizio, L.A.; Erdjument-Bromage, H.; Taylor-Papadimitriou, J.; Tempst, P.; Zhang, Y. PLU-1 is an H3K4 demethylase involved in transcriptional repression and breast cancer cell proliferation. *Mol. Cell,* **2007,** *25*(6), 801-812.

[121] Wang, J.K.; Tsai, M.C.; Poulin, G.; Adler, A.S.; Chen, S.; Liu, H.; Shi, Y.; Chang, H.Y. The histone demethylase UTX enables RB-dependent cell fate control. *Genes. Dev.,* **2010,** *24*(4), 327-332.

[122] van Haaften, G.; Dalgliesh, G.L.; Davies, H.; Chen, L.; Bignell, G.; Greenman, C.; Edkins, S.; Hardy, C.; O'Meara, S.; Teague, J.; Butler, A.; Hinton, J.; Latimer, C.; Andrews, J.; Barthorpe, S.; Beare, D.; Buck, G.; Campbell, P.J.; Cole, J.; Forbes, S.; Jia, M.; Jones, D.; Kok, C.Y.; Leroy, C.; Lin, M.L.; McBride, D.J.; Maddison, M.; Maquire, S.; McLay, K.; Menzies, A.; Mironenko, T.; Mulderrig, L.; Mudie, L.; Pleasance, E.; Shepherd, R.; Smith, R.; Stebbings, L.; Stephens, P.; Tang, G.; Tarpey, P.S.; Turner, R.; Turrell, K.; Varian, J.; West, S.; Widaa, S.; Wray, P.; Collins, V. P.; Ichimura, K.; Law, S.; Wong, J.; Yuen, S.T.; Leung, S.Y.; Tonon, G.; DePinho, R.A.; Tai, Y.T.; Anderson, K.C.; Kahnoski, R.J.; Massie, A.; Khoo, S.K.; Teh, B.T.; Stratton, M.R.; Futreal, P.A. Somatic mutations of the histone H3K27 demethylase gene UTX in human cancer. *Nat. Genet.,* **2009,** *41*(5), 521-523.

[123] Lynch, J.T.; Harris, W.J.; Somervaille, T.C. LSD1 inhibition: a therapeutic strategy in cancer? *Expert. Opin. Ther. Targets,* **2012,** *16*(12), 1239-1249.

[124] Zhang, K.; Dent, S.Y. Histone modifying enzymes and cancer: going beyond histones. *J. Cell Biochem.,* **2005,** *96*(6), 1137-1148.

[125] Carbone, M.; Yang, H.; Pass, H.I.; Krausz, T.; Testa, J.R.; Gaudino, G. BAP1 and cancer. *Nat. Rev. Cancer,* **2013,** *13*(3), 153-159.

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