Mutations of Chromatin Structure Regulating Genes in Human Malignancies

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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.

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, BBRM1, 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
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 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 melamomas 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%          |
| 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%          |
| Cholangiocarcinoma | Intrahepatic Cholangiocarcinoma (Johns Hopkins University, Nature Genetics 2013) | 6                | 40          | 15.0%          |
| Cholangiocarcinoma | Cholangiocarcinoma (National Cancer Centre of Singapore, Nature Genetics 2013) | 4                | 15          | 26.7%          |
| Cholangiocarcinoma | Cholangiocarcinoma (National University of Singapore, Nature Genetics 2012) | 1                | 8           | 12.5%          |
| Colorectal| Colorectal Adenocarcinoma (Genentech, Nature 2012) | 5                | 72          | 6.9%          |
| Colorectal| 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    | 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%          |
| Gene | Cancer type | Data source | No. of mutations | No. of total | % of mutations |
|------|-------------|-------------|------------------|--------------|----------------|
| **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 | 6.6% |
| | | 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% |
| Gene   | Cancer type         | Data source                                                                 | No. of mutations | No. of total | % of mutations |
|--------|---------------------|------------------------------------------------------------------------------|------------------|--------------|---------------|
| 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  | 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%          |
| 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%          |
|        | Cholangiocarcinoma  | Intrahepatic Cholangiocarcinoma (Johns Hopkins University, 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%          |
|        | Cholangiocarcinoma  | Cholangiocarcinoma (National Cancer Centre of Singapore, Nature Genetics 2013) | 1                | 15           | 6.7%          |
|        | Colorectal          | Colorectal Adenocarcinoma (Genentech, Nature 2012)                          | 10               | 72           | 13.9%         |
| 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 (TCGA, 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.

SMARC3 (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]. RSF1 is 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        | Lung                      | Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)| 2                | 42           | 4.8%           |
| (RbAP48)     | Prostate                  | Prostate Adenocarcinoma, Metastatic (Michigan, Nature 2012)| 3                | 61           | 4.9%           |
| RBBP7        | Cholangiocarcinoma        | Cholangiocarcinoma (National University of Singapore, Nature Genetics 2012)| 1               | 8            | 12.5%          |
| (RbAP46)     |                           |                                                             |                  |              |                |
| 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      | Colorectal                | Colorectal Adenocarcinoma (Genentech, Nature 2012)        | 4                | 71           | 5.6%           |
| (ISWI, SNF2H)| Uterine                   | Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013) | 13               | 250          | 5.2%           |
| SMARCA1      | Cholangiocarcinoma        | Cholangiocarcinoma (National University of Singapore, Nature Genetics 2012)| 1               | 8            | 12.5%          |
| (SNF2L)      |                           |                                                             |                  |              |                |
|              | 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         | Stomach Adenocarcinoma (TCGA, Nature 2014)        | 18                                                                         | 290              | 6.2%         |
| Stomach         | 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 (RUVB1) and RUVBL2 (RUVB2) 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 ERCC5 may 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%          |
|      | Stomach                   | Stomach Adenocarcinoma (UHK, Nature Genetics 2011) | 2                | 22          | 9.1%          |
| CDH2 | Bladder                   | Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013) | 4                | 100         | 4.0%          |
|      | Colorectal                | Colorectal Adenocarcinoma (TCGA, Nature 2014)    | 9                | 225         | 4.0%          |
|      | Stomach                   | Stomach Adenocarcinoma (UHK, Nature Genetics 2011) | 2                | 22          | 9.1%          |
|      | Colorectal                | Colorectal Adenocarcinoma (TCGA, Nature 2012)    | 3                | 71          | 4.2%          |
|      | Stomach                   | Stomach Adenocarcinoma (TCGA, Provisional)       | 10               | 222         | 4.5%          |
|      | Stomach                   | Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014) | 4                | 100         | 4.0%          |
|      | 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%          |
|      | Stomach                   | Stomach Adenocarcinoma (TCGA, Nature 2014)       | 10               | 222         | 4.5%          |
|      | Stomach                   | Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014) | 4                | 100         | 4.0%          |
|      | Stomach                   | Stomach Adenocarcinoma (TCGA, Provisional)       | 14               | 222         | 6.3%          |
|      | Stomach                   | 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%          |
|      | Lung                      | Lung Adenocarcinoma (Broad, Cell 2012)           | 4                | 182         | 2.2%          |
|      | Lung                      | Lung Adenocarcinoma (TCGA, Nature 2014)          | 6                | 231         | 2.6%          |
|      | Melanoma                  | Melanoma (Broad/Dana Farber, Nature 2012)         | 2                | 25          | 8.0%          |
|      | Melanoma                  | Cutaneous Melanoma (Broad, Cell 2012)            | 11               | 121         | 9.1%          |
|      | Melanoma                  | Cutaneous Melanoma (Yale, Nature Genetics 2012)   | 6                | 91          | 6.6%          |
|      | Stomach                   | Stomach Adenocarcinoma (TCGA, Nature 2014)       | 26               | 289         | 9.0%          |
|      | Stomach                   | 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%          |
| Gene   | Cancer type             | Data source                                                                 | No. of mutations | No. of total | % of mutations |
|--------|-------------------------|------------------------------------------------------------------------------|------------------|--------------|----------------|
|        |                         | Cutaneous Melanoma (Broad, Cell 2012)                                       | 9                | 122          | 7.4%           |
|        |                         | CDH6 Bladder Urothelial Carcinoma (BGI, Nature Genetics 2013)                | 5                | 98           | 5.1%           |
|        |                         | CDH6 Bladder Urothelial Carcinoma (TCGA, Nature 2014)                       | 10               | 130          | 7.7%           |
|        | Colorectal              | Colorectal Adenocarcinoma (Genentech, Nature 2012)                          | 9                | 72           | 12.5%          |
|        |                         | CDH6 Colorectal Adenocarcinoma (TCGA, Nature 2012)                          | 16               | 225          | 7.1%           |
|        | Lung                    | Lung Adenocarcinoma (Broad, Cell 2012)                                     | 9                | 184          | 4.9%           |
|        |                         | CDH6 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                | CDH6 Cutaneous Melanoma (Broad, Cell 2012)                                  | 11               | 121          | 9.1%           |
|        |                         | CDH6 Cutaneous Melanoma (Yale, Nature Genetics 2012)                        | 6                | 91           | 6.6%           |
|        | Melanoma                | Melanoma (Broad/Dana Farber, Nature 2012)                                   | 2                | 25           | 8.0%           |
|        | Prostate                | CDH6 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                 | CDH7 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 Urothelial Carcinoma (TCGA, Nature 2014)                       | 13               | 130          | 10.0%          |
|        | Colorectal              | CDH7 Colorectal Adenocarcinoma (Genentech, Nature 2012)                     | 7                | 72           | 9.7%           |
|        |                         | CDH7 Colorectal Adenocarcinoma (TCGA, Nature 2012)                          | 9                | 225          | 4.0%           |
|        | Lung                    | CDH7 Lung Adenocarcinoma (Broad, Cell 2012)                                 | 11               | 183          | 6.0%           |
|        |                         | CDH7 Lung Adenocarcinoma (TCGA, Nature 2014)                                | 12               | 231          | 5.2%           |
|        | Medulloblastoma         | CDH7 Medulloblastoma (PCGP, Nature 2012)                                    | 3                | 37           | 8.1%           |
|        | Melanoma                | CDH7 Cutaneous Melanoma (Broad, Cell 2012)                                  | 6                | 120          | 5.0%           |
|        |                         | CDH7 Melanoma (Broad/Dana Farber, Nature 2012)                              | 3                | 25           | 12.0%          |
|        | Stomach                 | CDH8 Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014)          | 5                | 100          | 5.0%           |
|        |                         | Stomach Adenocarcinoma (TCGA, Nature 2014)                                  | 27               | 290          | 9.3%           |
|        | Uterine                 | CDH8 Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013)              | 20               | 247          | 8.1%           |
|        | Colorectal              | CDH8 Colorectal Adenocarcinoma (Genentech, Nature 2012)                     | 7                | 72           | 9.7%           |
|        | Esophagus               | CDH8 Esophageal Adenocarcinoma (Broad, Nature Genetics 2013)                | 6                | 146          | 4.1%           |
|        | Head & neck             | CDH8 Head and Neck Squamous Cell Carcinoma (Broad, Science 2011)            | 3                | 73           | 4.1%           |
|        | Lung                    | CDH8 Lung Adenocarcinoma (TCGA, Nature 2014)                                | 12               | 231          | 5.2%           |
|        |                         | CDH8 Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012)            | 3                | 42           | 7.1%           |
|        |                         | CDH8 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                              | 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 in INO80/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%       |
| 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%        |
Mutations of Chromatin Structure Regulating Genes

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 melanoma, 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 melanoma 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.

| 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  | 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  | Colorectal             | Colorectal Adenocarcinoma (Genentech, Nature 2012)                         | 4                | 71           | 5.6%           |
|        | Lung                   | Small Cell Lung Cancer (CLCGP, Nature Genetics 2012)                        | 2                | 29           | 6.9%           |
| INO80D | Stomach                | Stomach Adenocarcinoma (TCGA, Nature 2014)                                 | 13               | 289          | 4.5%           |
|        | (FLJ20309)             | Stomach Adenocarcinoma (UHK, Nature Genetics 2011)                          | 1                | 22           | 4.5%           |
| MCR5I  | Stomach                | Stomach Adenocarcinoma (UHK, Nature Genetics 2011)                          | 3                | 71           | 4.2%           |
| RUVBL2 | Colorectal             | Colorectal Adenocarcinoma (Genentech, Nature 2012)                         | 1                | 25           | 4.0%           |
|        | Stomach                | Stomach Adenocarcinoma (UHK, Nature Genetics 2011)                          | 1                | 22           | 4.5%           |
| ACTR6  | Melanoma               | Melanoma (Broad/Dana Farber, Nature 2012)                                   | 5                | 122          | 4.1%           |
| CFDP1  | Stomach                | Stomach Adenocarcinoma (UHK, Nature Genetics 2011)                          | 5                | 122          | 4.1%           |
| 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.
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 acetyltransferases      | 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                      | KAT6B (MYST4) | Colorectal                                      | Colorectal Adenocarcinoma (Genentech, Nature 2012) | 3                | 71           | 4.2%           |
|                                 |            | Colorectal                                      | 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%           |
|                                 |            | Lung                                            | Small Cell Lung Cancer (Johns Hopkins, Nature Genetics 2012) | 2                | 42           | 4.8%           |
|                                 |            | Melanoma                                        | Lung Squamous Cell Carcinoma (TCGA, Nature 2012)  | 10               | 179          | 5.6%           |
|                                 |            | Melanoma                                        | Cutaneous Melanoma (Broad, Cell 2012)           | 11               | 121          | 9.1%           |
|                                 |            | Melanoma                                        | Cutaneous Melanoma (Yale, Nature Genetics 2012)  | 4                | 91           | 4.4%           |
|                                 |            | Melanoma                                        | Melanoma (Broad/Dana Farber, Nature 2012)        | 3                | 25           | 12.0%          |
|                                 |            | Stomach                                         | Stomach Adenocarcinoma (TCGA, Nature 2014)       | 22               | 289          | 7.6%           |
|                                 |            | Stomach                                         | 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 Adenocarcinoma (Genentech, Nature 2012) | 7                | 72           | 9.7%           |
|                                 |            | Colorectal                                      | 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%           |
|                                 |            | Melanoma                                        | Cutaneous Melanoma (Yale, Nature Genetics 2012)  | 5                | 91           | 5.5%           |
|                                 |            | Melanoma                                        | Melanoma (Broad/Dana Farber, Nature 2012)        | 2                | 25           | 8.0%           |
|                                 |            | Prostate                                        | Prostate Adenocarcinoma, Metastatic (Michigan, Nature 2012) | 3                | 61           | 4.9%           |
| Subgroup | Gene       | Cancer type                      | Data source                                      | No. of mutations | No. of total | % of mutations |
|----------|------------|----------------------------------|-------------------------------------------------|------------------|--------------|----------------|
| Stomach  | Stomach Adenocarcinoma (TCGA, Nature 2014) | 17 | 288 | 5.9%          |
| Uterine  | 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%          |
| 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  | 42  | 4.8%          |
| EP300    | 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%          |
| 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) |  | 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% |
| Subgroup                        | Gene     | Cancer type                        | Data source                                      | No. of mutations | No. of total | % of mutations |
|--------------------------------|----------|------------------------------------|--------------------------------------------------|------------------|--------------|----------------|
| EZH2                           | AML      | Acute Myeloid Leukemia (TCGA, NEJM 2013) | 8                                                 | 29               | 27.6%        |
|                                |          | Bladder Cancer (MSKCC, Eur Urol 2014) | 3                                                 | 30               | 10.0%        |
|                                |          | Bladder Urothelial Carcinoma (TCGA, Nature 2014) | 4                                                 | 41               | 9.7%         |
|                                |          | Breast Invasive Carcinoma (TCGA, Nature 2012) | 4                                                 | 63               | 6.3%         |
|                                |          | 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 (TCGC, Nature 2014) | 1                                                 | 20               | 5.0%         |
|                                | Glioblastoma | Glioblastoma (TCGA, Cell 2013) | 6                                                 | 122              | 4.9%         |
|                                | Head & neck | Head and Neck Squamous Cell Carcinoma (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, Nature Genetics 2012) | 2                                                 | 29               | 6.9%         |
|                                | Stomach   | Stomach Adenocarcinoma (TCGA, Nature 2014) | 13                                                | 289              | 4.5%         |
|                                |          | Stomach Adenocarcinoma (UHK, Nature 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%         |
| 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 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 (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 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 Adenocarcinoma (UHK, Nature Genetics 2011) | 1                                               | 22               | 4.5%         |
|                       | PRMT5         | Head and Neck Squamous Cell Carcinoma (Broad, Science 2011)| 3                                              | 73               | 4.1%         |
| 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%           |
| Subgroup | Gene | Cancer type | Data source | No. of mutations | No. of total | % of mutations |
|----------|------|-------------|-------------|------------------|--------------|---------------|
| Medulloblastoma (PCGP, Nature 2012) | Stomach | Stomach Adenocarcinoma (Pfizer and UHK, Nature Genetics 2014) | 3 | 37 | 8.1% |
| Stomach Adenocarcinoma (TCGA, Nature 2014) | Stomach Adenocarcinoma (UHK, Nature Genetics 2011) | 12 | 286 | 4.2% |
| Stomach Adenocarcinoma (TCGA, Nature 2013) | Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013) | 11 | 250 | 4.4% |
| KDM1B (LSD2) | Stomach | Stomach Adenocarcinoma (TCGA, Nature 2014) | 13 | 289 | 4.5% |
| Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013) | Uterine | 13 | 250 | 5.2% |
| Other histone modification enzymes | RPS6KA5 (MSK1) | Colorectal Adenocarcinoma (Genentech, Nature 2012) | 3 | 71 | 4.2% |
| Melanoma | Melanoma (Broad/Dana Farber, Nature 2012) | 1 | 25 | 4.0% |
| Stomach Adenocarcinoma (UHK, Nature Genetics 2011) | Stomach | 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 Adenocarcinoma (UHK, Nature Genetics 2011) | Stomach | 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) | Cholangiocarcinoma | 37 | 425 | 8.7% |
| Intrahepatic Cholangiocarcinoma (Johns Hopkins University, Nature Genetics 2013) | Cholangiocarcinoma (National Cancer Centre of Singapore, Nature Genetics 2013) | 7 | 40 | 17.5% |
| Nasopharyngeal Carcinoma (Singapore, Nature Genetics 2014) | NPC | 4 | 15 | 26.7% |
| Stomach Adenocarcinoma (TCGA, Nature 2014) | Stomach | 12 | 286 | 4.2% |
| Uterine Corpus Endometrioid Carcinoma (TCGA, Nature 2013) | Uterine | 10 | 250 | 4.0% |
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 mutations 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 demethylases 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%).

| Subgroup | Gene | Cancer type | Data source | No. of mutations | No. of total | % of mutations |
|----------|------|------------|-------------|-----------------|-------------|---------------|
| RNF20    | Colorectal | Colorectal Adenocarcinaoma (Genentech, Nature 2012) | 4 | 71 | 5.6% |
| Melanoma | Cutaneous Melanoma (Broad, Cell 2012) | 6 | 120 | 5.0% |
| Melanoma | 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 Adenocarcinaoma (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.
2.3. 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 tone variant H2AX. They have important functions in DNA ribosylation, have been observed on H1, H2B, H3, and histone ubiquitination, sumoylation and poly-ADP-ribosylation 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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