**Heterochromatin modifiers list – Cuppen group**

|  |  |  |
| --- | --- | --- |
| **Type** | **Name** | **Mark** |
| Readers | **HP1a** | H3K9me |
| MPP8 | H3K9me |
| TRIM28 | H3K9me |
| MeCP2 | DNA methylation |
| Erasers | KDM1A | H3K4me |
| KDM1B | H3K4me |
| KDM3A | H3K9me |
| KDM3B | H3K9me |
| JMJD1C (KDM3C) | H3K9me |
| **KDM4A** | H4K36, H3K9, H3K36me |
| KDM4B | H3K9, H3K36, H1.4K26, H4K20me |
| KDM4C | H3K9, H3K36me |
| KDM4D | H3K9 |
| SIRT1 | H4K16 and SUV39H1ac |
| SIRT2 | H4K20, H4K16ac |
| SIRT3 | H3K9, H4K16ac |
| SIRT6 | H3K9ac |
| SIRT7 | H3K18ac |
| LSD1 (KDM1A) | H3K4me |
| LSD2 (KDM1B) | H3K4me |
| UTX | H3K27me |
| Writers | **EZH2** | H3K27me |
| SETD1A | H3K4me |
| **SETDB1** | H3K9me |
| **SUV39H1/2** | H3K9me |
| G9a | H3K9me |
| GLP | H3K9me |
| Tip60 | H4K12ac, proteins |
| CK2 | Phosphorylation of HP1 |
| SMYD3 | H3K4me2/3 |
| DNMT1 | DNA methylator |
| DNMT3A | DNA methylator |
| DNMT3B | DNA methylator |
| Cofactors | Pax3 | binds promotors |
| ATF7IP | SETDB1, me2>me3 |
| TRIM28 | SETDB1, HP1a, HUSH complex |
| Piwi | Binds piRNA and HP1a |
| ATRX | Transcriptional regulator, retrotransposon silencing |
| Others | SMC5 & 6 | DNA binding |
| Lamin A/C (LMNA) | Tethering to the nuclear envelope |
| Lamin B (LMNB1) | Tethering to the nuclear envelope |

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| --- | --- | --- | --- | --- | --- | --- |
| Gene | Function | Cancer type | Alteration | Chromosome effect | cBioPortal  (TCGA) | Ref. |
| HP1  *cHet*  (CBX5, CBX1, CBX3) | **Reader**  Binds methylated H3K9, forms a platform for effector binding | Metastatic phenotype in breast cancer | Downregulation  mRNa and protein |  | 1% of queried patients  -  Most frequent adrenocortical carcinoma (4.4%) | 12 |
| Breast tumor | Decreased expression level of HP1sa |  | 3,4 |
| Melanoma | Decreased expression level of HP1b |  | 5 |
| Lymphomas | Decreased level at centromeres | Chromosome segregation defects | 6 |
| Breast cancer | Decreased expression of HP1Hsalpha |  |
| Brain cancer (embryonal) |
| Colon cancer |
| Papillary thyroid carcinoma |
| Leukemia | Decreased expression of HP1Hsalpha, HP1Hsbeta, HP1Hsgamma |  |
| Ovarian cancer | Decreased expression of HP1Hsgamma |  |
| Colorectal cancer | Upregulation of HP1Hsgamma |  | 7 |
| KDM1A (LSD1) | **Eraser**  Mono- dimethyl H3K4 demethylase | Aggressive prostate cancer (marker for tumor recurrence) | High expression of LSD1 |  | 1% of queried patients  -  Most frequent Cervical Adenocarcinoma (4.35%) | 8 |
| Poorly differentiated neuroblastoma |  |
| Estrogen receptor negative breast cancer |  |
| KDM1B (LSD2) | **Eraser**  (Mono-) dimethyl H3K4 demethylase | Malignant breast cell lines | Elevated expression |  | 2% of queried patients  -  Most frequent Bladder urothelial carcinoma (8.52%, 6.57% amplification) | 9 |
| Pancreatic cancer | Increased expression (staining) |  | 10 |
| KDM3A | **Eraser**  Mono- and dimethyl H3K9 demethylase | Hepatocellular carcinoma | Higher expression |  | 2% of queried patients  -  Most frequent Melanoma (5.41%) | 11 |
| Colorectal cancer | Overexpressed |  | 12 |
| Breast cancer |  |
| Bladder carcinoma | Elevated expresion |  | 13 |
| KDM3B | **Eraser**  Mono- and dimethyl H3K9 demethylase | Leukemia cell line | Higher expressed |  | 3% of queried patients  -  Most frequent endometrial carcinoma (11.09%) | 14 |
| Lymphoma cell line |  |
| Acute Myeloid Leukemia |  |
| JMJD1C (KDM3C) | **Eraser**  Mono- and dimethyl H3K9 demethylase | Colon rectal cancer | Upregulated |  | 4% of queried patients  -  Most frequent endometrial carcinoma (11.77%) | 15 |
| KDM4A  (JMJD2A) | **Erasing**  Demethylates H4K36me2/me3, H3K9me2/3, H3K36me2/3 | Breast tumor | Overexpression of KDM4A |  | 2% of queried patients  -  Most frequent endometrial carcinoma (8%) | 16 |
| Lung cancer | Overexpression of KDM4A |  | 17 |
| Prostate cancer | Overexpression of KDM4A |  | 8,18 |
| Colorectal cancer | Overexpression of KDM4A |  |
| Lung cancer | Overexpression of KDM4A |  |
| Breast cancer | Overexpression of KDM4A |  |
| Squamous cell carcinoma | Overexpression of KDM4A |  |
| Bladder | Overexpression of KDM4A in early stage of carcinogenesis |  |
| Triple negative breast cancer | Elevated expression of KDM4A | Altered pattern of H3K9me3 at pericentromeric heterochromatin | 19 |
| KDM4B (JMJD2B) | **Eraser**  Demethylase of H3K9/36me2/3, H1.4K26me3 and H4K20me2 | Triple negative breast cancer | Overexpressed |  | 2% of queried patients  -  Most frequent sarcoma (8.24%, 5.49% amplification) | 19,20 |
| Gastric cancer |  | 21 |
| ER-positive breast cancer |  | 22 |
| Bladder cancer |  | 20,23 |
| Lung cancer |  |
| Colonrectal cancer |  |  |
| KDM4C  (JMJD2C/ GASC1) | **Eraser**  Demethylase of H3K9/36me2/3 | Esophageal squamous cell carcinoma (cell line) | Amplified KDM4C | ‘Activation of oncogenes, such as MYC’ | 3% of queried patients  -  Most frequent Esophageal Squamous Cell Carcinoma (8.42%) | 24 |
| Medulloblastoma |  | 24–26 |
| Breast cancer  (aggressive, basal-like) |  | 24,27 |
| Primary mediastinal B-cell Lymphoma |  | 24,28 |
| Hodgkin lymphomas |  |  |
| KDM4D (JMJD2D) | **Eraser**  Demethylase of H3K9me2/3 | Gastrointestinal stromal tumour | Upregulated |  | 2% of queried patients  -  Most frequent melanoma (6.31%) |  |
| SETD1A (yeast Set1) | **Writer**  Methyltransferase H3K4 | Breast cancer | Overexpressed |  | 3% of queried patients  -  Most frequent melanoma (11.04%) | 29 |
| ERa positive breast cancer | Upregulated |  | 30 |
| SETDB1 | **Writer**  Methyltransferase H3K9 involved in transcriptional silencing of euchromatic genes and retroelements | Non small and small lung cancer | Amplification of SETDB1 |  | 6% of queried patients  -  Most frequent endometrial carcinoma (14.5%) | 31 |
| Acute myeloid leukemia | Elevated expression in primary tumors |  | 32 |
| Melanoma | Amplification |  | 33 |
| Breast cancer | Overexpression of SETDB1  mRNA | Modulates epigenetic marks associated with aberrative  EMT-mediated gene expression | 34–36 |
| SUV39H1/2  *cHet* | **Writer**  H3K9me2/3 methyltransferase, marks repetitive sequences | Leukemia | Overexpression of SUV39H at gene, mRNA and protein level |  | 2% of queried patients  -  Most frequent undifferentiated stomach adenocarcinoma (7.7%) | 37,38 |
| Lymphomas |  |
| Lung cancer |  |
| Breast cancer |  |
| Colorectal cancer |  |
| Gastric cancer |  |
| Hepatocellular cancer |  |
| Lymphomas | Disruption of SUV39H | Loss of methylering at pericentric chromatin, impairing heterochromatin structures and genomic instability, appearances of alternative lengthening of telomeres (immortalizing) | 37–40 |
| EZH2  *fHet* | **Writer**  Part of the PRC2 complex, displays catalytic activity inducing mono, di and trimethylation on H3K27 | General | Elevated levels of EZH2 | Suppression of senescence in stress situations inducing genomic instability | 3% of queried patients  -  Most frequent endometrial carcinoma (8%) | 41 |
| Prostate cancer | Highly expressed |  | 42–44 |
| Lymphomas |  |
| Hematological malignancies | Overexpression |  |
| Pancreatic cancer |  |
| Bladder carcinoma |  |
| Gastric cancer |  |
| Lung cancer |  |
| Hepatocellular carcinoma |  |
| Glioblastoma multiforme |  |
| Cervical cancer |  |
| Ovarian cancer |  |
| Melanoma |  |
| Soft tissue sarcoma |  |
| Lymphoma |  |
| Colorectal cancer |  |
| Retinoblastoma |  |
| Tongue cancer |  |
| Peripheral nerve shealth tumors | Loss of function mutation |  |
| Myeloproliferative neoplasms |  |
| Myeloid –myelodysplastic malignancies |  |
| Pediatric tumors of the central nervous system |  |
| Leukemia |  |
| Aggressive and metastatic breast cancer | Overexpression | Decrease in the number of DNA repair foci (decreased expression of RAD51), increased aneuploidy | 45 |
| MPP8  (MPHOSPH8) | **Reader**  H3K9me binding protein | Carcinoma | Elevated expression |  | 2% of queried patients  -  Colorectal adenocarcinoma (6.4%) | 46 |
| Non small cell lung carcinoma | Increased expression |  | 47 |
| Gastric cancer | Increased expression |  | 48 |
| t (KAT5) | **Reader/ writer**  Acetyltransferase | Sporadic invasive breast adenocarcinoma cell line/ breast cancer data set | Low expression of Tip60 | Genomic instability (defective HR-directed DNA repair) | 2% of queried patients  -  Endometrial Carcinoma (5.8%) | 49,50 |
| Colorectal cancer (primary) | Downregulation of Tip60 | Accumulation of DSBs | 51 |
| Malignant pleural mesothelioma (inflammatory cancer) | KAT5 (Tip60) increased expression |  | 52 |
| Breast cancer | Low Tip60 mRNA expression > poor overall survival and relapse free survival |  | 53 |
| Lymphomas | Tip60 gene (HTATIP) mono allelic loss leading to reduction in mRNA levels |  | 54 |
| Head-and-neck carcinoma |
| Mammary carcinoma |
| G9a  (EHMT2) | **Writer**  H3K9me1/2 methyltransferase | Non-small cell lung cancer | Overexpression |  | 3% of queried patients  -  Most frequent mature b-cell neoplasms (8.33%) and esophagogastric adenocarcinoma (7%) | 55 |
| Hepatocellular carcinoma | Overexpressed |  | 56 |
| Superficial and invasive transitional cell carcinoma |  |
| B cell acute lymphoblastic leukemia |  |
| Primary colon carcinoma |  |
| Cutaneous melanoma |  |
| Prostate carcinoma |  |
| Ovarian serous adenocarcinoma |  |
| Lung adenocarcinoma |  |
| B cell chronic lymphocytic leukemia |  |
| Bladder cancer | Amplified |  | 57 |
| GLP  (EHMT1) | **Writer**  H3K9me1/2 methyltransferase | Astrocytoma | Overexpressed |  | 3% of queried patients  -  Most frequent Endometrial Carcinoma (7.85%) | 56 |
| Smoldering multiple myeloma |  |
| Head and neck cancer |  |
| Pax3 | **Reader**  Transcription factor associated with pericentromeric heterochromatin, interacts with HP1y and KAP1 | Neuroblastomas | Gain of function |  | 2% of queried patients  -  Most frequent Endometrial Carcinoma (4.44%) | 58,59 |
| Alveolar rhabdomyosarcomas |  |
| Glioblastomas | Overexpression |  |
| Melanoma |  |
| Gastric cancer |  |
| Thyroid cancer | Down regulated by promoter methylation |  | 59 |
| ATF7IP | **Cofactor of SETDB1**  Necessary for the conversion of H3K9me2 to me3 | Stomach adenocarcinoma | Overexpression (high tissue staining) |  | 3% of queried patients  -  Most frequent Endometrial Carcinoma (9.56%) | 60 |
| Invasive ductal carcinoma of the breast |  |
| Lung adenocarcinoma |  |
| Lung Squamous cell carcinoma |  |
| Piwi (PIWIL1-4) | Nuclear RNA-binding proteins | Colorectal cancer | Elevated expression of PIWIL1 |  | 3% of queried patients  -  Most frequent Melanoma (8.78%) | 61 |
| Breast cancer |
| Chronic myeloid leukemia |
| Hepatocellular carcinoma |
| Glioma |
| Esophageal squamous cell carcinoma |
| Soft tissue sarcoma |
| Gastric cancer |
| Ovarian cancer |
| Renal cell carcinoma |
| Colorectal cancer | Elevated expression of PIWIL2 |  |
| Ovarian cancer |
| Renal cell carcinoma |
| Glioma |
| Non-small cell lung cancer |
| Hilar cholangiocarcinoma |
| Bladder cancer |
| Melanoma | Elevated expression of PIWIL3 |  |
| Ovarian cancer |
| Breast cancer |
| Colorectal cancer |
| Gastric cancer |
| Ovarian cancer | Elevated expression of PIWIL4 |  |
| Breast cancer |
| Renal cell carcinoma |
| Colorectal cancer |
| Cervical cancer |
| SMC5/6 | **SMC5/6 complex**  DNA binding | Breast cancer | Increased level of SMC6 expression was related to high grade breast cancer |  | 2% of queried patients  -  Most frequent Melanoma (6.31%) | 62 |
| Brain metastases | Significantly mutated SMC5 (loss and high level gain) |  | 2% of queried patients  -  Most frequent Endometrial cancer (9.22%, 8.02% mutation) | 63 |
| SMYD3  (KMT3E) | **Writer**  H3K4me2/3 | Colorectal cancer | Upregulated |  | 4% of queried patients  -  Most frequent Invasive Breast Carcinoma (10.98%, almost all amplificiations) | 64,65 |
| Hepatocellular carcinoma |  |
| Breast cancer |  |
| Pancreatic cancer | Highly expressed |  | 66 |
| Prostate cancer |  |
| MeCP2 | **(DNA methylation) reader**  CpG island and MAR elements | Primary gastric cancer | Highly expressed |  | 3% of queried patients  -  Most frequent Mature B-cell neoplasms (10.42%)  -  18% overall frequency of amplification in all cancers 67 | 68 |
| Ovarian cancer | Amplification of MeCP2 |  | 67 |
| Triple negative breast cancer |  |
| Lung Adeno |  |
| Head and neck cancer |  |
| Lung squamous cancer |  |
| Cervical cancer |  |
| Liver cancer |  |
| Stomach cancer |  |
| Uterine cancer |  |
| SIRT1 | **Eraser**  Deacetylase of H4K16Ac and K266 of SUV39H1 inducing activity | Prostate cancer | Overexpression of SIRT1 (in old mice) |  | 1.4% of queried patients  -  Most frequent Endometrial Carcinoma (4.95%)  -  5/106 mutations at R649C/H | 69 |
| Low level of SIRT1 > decreased recurrence-free survival |  | 69,70 |
| Advanced prostate cancer | Highly expressed,  Promotes cell invasion, migration and metastasis through MMP2, ZEB1 and cortactin |  | 69,71 |
| Breast cancer | Upregulation > inactivation of tumor suppressor HIC1 |  | 69,72 |
| Invasive ductal carcinoma | Upregulated > positively regulates the expression of aromatase |  | 69,73 |
| Non-small-cell lung cancer | Positive SIRT1 expression (low p53 acetylation) |  | 69,74 |
| Colorectal cancer (malignant) | Increased SIRT1 protein level (high expression of cMYC) | Microsatellite instability | 69,75,76 |
| Thyroid cancer | Overexpressed SIRT1 (correlated with cMYC protein levels) |  | 69,77 |
| Gastric cardiac carcinoma (with lymphatitc metastasis) | Overexpressed SIRT1 |  | 69,78 |
| Hepatocellular carcinoma | Elevated SIRT1 expression |  | 69,79 |
| Pancreatic cancer | Overexpression |  | 69,80 |
| Malignant ovarian epithelial tumors | Increased expression of SIRT1 |  | 69,81 |
| Leukemia | Overexpression |  | 69,82,83 |
| SIRT2 | **Eraser**  modulating the mitotic deposition of H4K20 methylation by deacetylation of H4K16ac and to a much lesser extent H3K9Ac | Glioma | Reduced expression | 19q deletions (SIRT2 is located at 19q13.2) | 2.7% of queried patients  -  Most frequent Ovarian epithelial tumor (9.42%) | 69,84 |
| Esophageal/ gastric adenocarcinomas | Reduced expression |  | 69,85 |
| SIRT3 | **Eraser**  Primarily mitochondrial, nuclear deacetylase of H3K9 and H4K16Ac | Breast carcinoma | Reduced SIRT3 levels (mainly deletions) |  | 1% of queried patients  -  Most frequent Seminoma (4.76%, all deep deletion) | 69,86 |
| Colon carcinoma |  |
| Head and Neck Squamous cell carcinoma |  | 69,87 |
| Hepatocellular carcinoma |  | 69,88 |
| Osteosarcoma |  | 69,89 |
| Lymph node positive breast cancer | High SIRT3 expression |  | 69,90 |
| Oral squamous cell carcinoma |  | 69,91 |
| SIRT6 | **Eraser**  H3K9Ac deacetylase that modulates telomeric chromatin and promotes DNA DSB repair | Pancreatic cancer | Downregulated SIRT6 |  | 1.2% of queried patients  -  Most frequent Sarcoma (4.71%) | 69,92 |
| Colorectal cancer |  |
| Hepatocellular carcinoma |  |
| Head and Neck Squamous cell carcinoma | Decreased expression of SIRT6 |  | 69,87 |
| Chronic Lymphocytic Leukemia | Increased SIRT6 mRNA levels |  | 69,93 |
| SIRT7 | **Eraser**  H3K18Ac deacetylase, regulations the repression of transcription of a set of non-nuclear genes. | Breast cancer | Increased SIRT7 expression |  | 2.2% of queried patients  -  Most frequent Hepatocellular Carcinoma (4.88%) | 69 |
| Thyroid cancer | Overexpressed SIRT7 |  | 69,94 |
| Head and Neck Squamous cell carcinoa | Lower mRNA expression |  | 69,87 |
| KAP1 (TRIM28) | **Reader/ Cofactor**  Corepressor of Pax3 and HP1, can bind to H3K9me | Prometastatic cervival cancer | Higher gene expression |  | 2% of queried patients  -  Most frequent Endometrial carcioma (6.14%) | 95 |
| Gastric cancer | Upregulation |  |
| Ovarian cancer | High expression level |  |
| Hepatocellular carcinoma | Increased mRNA and protein levels |  |
| Invasive breast carcinoma | Upregulation |  |
| UTX (KDM6A) | **Eraser**  H3K27me2/3 demethylase | Acute myelogenous leukemia | Inactivating mutations |  | 5% of queried patients  -  **Most frequent Bladder Urothelial Carcinoma (29.2%, 25.55% mutation)**  **-**  **9/404 mutations Q555\*** | 96 |
| Bladder transitional cell carcinoma |  |
| Breast acantholytic squamous carcinoma |  |
| Breast adenocarcinoma |  |
| Chronic myelogenous leukemia |  |
| Colorectal adenocarcinoma |  |
| Endometrial adenocarcinoma |  |
| Gliobastoma |  |
| Hodgkin lymphoma |  |
| Multiple myeloma |  |
| non-snall cell lung cancer |  |
| esophageal squamous cell carcinoma |  |
| Pancreatic adenocarcinoma |  |
| renal cell carcinoma |  |
| small-cell lung carcinoma |  |
| T-cell acute lymphoblastic leukemia |  |
| Urothelial carcinoma | Deleterious mutation |  | 97 |
| Multiple myeloma | Inactivating mutation |  | 98 |
| CK2  (CSNK2A1, CSNK2A2, CSNK2B) | **Writer**  Phosphorylating kinase | Leukemia | Increased expression |  | 4% of queried patients  -  Most frequent Mature B-cell neoplasm (14.58%) | 99,100 |
| Lymphoma |  |
| Squamous Cell carcinoma |  |
| Colon/ Kidney/ Prostate adenocarcinoma |  |
| DNMT1 | **Writer**  DNA methyltransferase | Breast cancer | Overexpression |  | 3% of queried patients  -  Most frequent endometrial carcinoma (11.6%) | 101 |
| Liver cancer | Overexpression |  | 102 |
| Pancreas cancer | Overexpression |  | 103 |
| Esophagus cancer | Overexpression |  | 104 |
| DNMT3A | **Writer**  DNA methyltransferase | Acute Myeloid Leukemia (mouse) | Deletion |  | 3% of queried patients  -  **Most frequent Leukemia (25%)** | 105 |
| Liver cancer | Overexpression |  | 106 |
| DNMT3B | **Writer**  DNA methyltransferase | Breast cancer | Overexpression |  | 3% of queried patients  -  Most frequent colorectal adenocarcinoma (11.62%) | 107 |
| Acute Myeloid Leukemia (mouse) | Deletion |  | 108 |
| Colon cancer | Overexpression |  | 109 |
| Prostate cancer | Overexpression |  | 110 |
| Lamin A/C (LMNA) | **Cofactor**  Tethering heterochromatin to the nuclear envelope111 | Early stage breast cancer | Reduced expression is linked with poor prognosis and larger tumour size |  | **4% of queried patients**  **-**  **Most frequent endometrial carcinoma (12.29%, mutations in all the cancers mostly consist out of amplifications)** | 112 |
| Colorectal cancer | Increased expression |  | 113 |
| Gastrointestinal cancer | Reduced expression |  |
| Esophagus cancer |  |
| Cervical cancer |  |
| Uterine cancer |  |
| Lamin B (LMNB1) | **Cofactor**  Tethering heterochromatin to the nuclear envelope111 | Hepatocellular carcinoma | Elevated expression |  | 1% of queried patients  -  Most frequent renal clear cell carcinoma (4.11%, all amplifications) | 113 |
| Breast cancer | Decreased expression indicated a poor prognosis |  |
| Lung cancer | Lower expression |  | 114 |

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