**Supplementary materials**

**Table 1**. PEV modifiers in *Drosophila*, human and mice, and associated pathways and human diseases.

*\** from[1] with additions accordingly <http://flybase.org/> and <https://www.uniprot.org/>

*\*\** from[2]

“–” - no data

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***Drosophila* (gene)** | **Mouse (protein)** | **Human (protein)** | **Function\*** | **Diseases \*\*** | **Pathways \*\*** | **References** |
| **Histone variants** | *H1* | H1.0 | H1.0 | Linker histone | – | – | [3] |
| *His2Av* | H2a/Za | H2A.Z | Heterochromatin-specific Н2a variant | – | – | [4] |
| **Histone modifiers** | *Su(var)3-1* (*JIL1*) | RPS6KA5 | RPS6KA5 | H3S10 serine/threonine phosphatase | – | – | [5, 6] |
| *Su*(*var*)*3*-*9* | SUV39H 1 (KMT1A)  SUV39H 2 (KMT1B) | SUV39H1 (KMT1A) | H3K9 histone methyltransferase, binds НР1 | Facioscapulohumeral muscular dystrophy (FSHD).  Retinoblastoma, lung adenocarcinoma, breast cancer. | Steroid hormones/nuclear receptors;  TGF-β/BMP/Smad; Hedgehog;  TNF-α/NF-κB. | [7] |
| *Su(var)4-20* | SUV420H 1 (KMT5B)  SUV420H 2 (KMT5C) | SUV420H1(KMT5B) SUV420H2 (KMT5C) | H4K20 histone methyltransferase | – | – | [8-10] |
| *eggless* | SETDB1 | SETDB1 | H3K9 histone methyltransferase | – | – | [11, 12] |
| *HDAC3*, *HDAC4*, *HDAC6* | HDAC2b | HDAC2 | Histone deacetylase | Chronic obstructive pulmonary disease (COPD), asthma. Prostate, breast, kidney, gastric, colorectal, ovarian, endometrial cancer. | Steroid hormones/nuclear receptors; WNT/β-catenin; Hedgehog. | [13] |
| *Su(var)3-64B* (*HDAC1*, *RPD3*) | HDAC1 | HDAC1 | H3K9 deacetylase | Schizophrenia. Prostate, breast, kidney, gastric, colorectal, ovarian, endometrial cancer. | Steroid hormones/nuclear receptors;  TGF-β/BMP/Smad; Hedgehog;  TNF-α/NF-κB. | [14, 15] |
| *Su(var)3-3* | KDM1A | KDM1A | H3K4me3 demethylase | – | – | [16, 17] |
| *Su(var)3-6* | PPP1CC | PPP1CC | PP1, serine/threonine phosphatase | – | – | [18] |
| *Ial* (*aurora B*) | PPP1CC | PPP1CC | H3S28 phosphatase | – | – | [19] |
| *Chm* (*chameau*) | KAT7 | KAT7 | Myst-domain histone deacetylase, Su(var), enhancer of Polycomb repression | – | – | [20] |
| *Sce* | RNF2c | RING2 | H2A Lys118 ubiquitin ligase |  |  | [21] |
| **Chromatin proteins** | *Su(var)2-5* (*HP1*) | HP1α,  HP1β | HP1A,  HP1B | Binds 2- and 3-methylated H3K9 and Su(var)3-9 | – | – | [22, 23] |
| *Su*(*var*)*2*-*HP2* | – | – | Binds HР1, enriched in heterochromatin | – | – | [24] |
| *Dom* (*Domina*) | – | – | Enriched in heterochromatin | – | – | [25] |
| *Pc* | CBX8 | CBX8 | Polycomb-complex component | – | – | [21, 26] |
| *Psc* | BMI1 | BMI1 | Polycomb-complex component | – | – | [21, 27] |
| *ph-d*, *ph-p* | PHC2, PHC3 | PHC2, PHC3 | Polycomb-complex component | – | – | [21] |
| *DLP* | DAXX | DAXX | – | – | – | [28] |
| *Ssrp* | SSRP1 | SSRP1 | – | – | – | [28] |
| – | TRIM28  (TIF1B, MommeD9) | TRIM28 (TIF1B) | KRAB-ZFPs corepressor | Breast cancer. | Steroid hormones/nuclear receptors;  G protein–coupled receptors and  receptor tyrosine kinases  (ERK/MAPK, PI3K/AKT,  JAK/STAT, JNK, PKC). | [29-31] |
| **Chromatin remodeling** | *dAtrx* (*XNP*) | ATRX | ATRX | – | ATRX syndrome, α-thalassemia myelodysplasia  syndrome.  Acute myeloid leukemia. | – | [32] |
| *Acf1* | BAZ1Ba  (ACF1, WSTF180)  BAZ1B  (WSTF, MommeD10) | BAZ1B (WSTF) | – | Williams-Beuren syndrome. | Steroid hormones/nuclear receptors. | [33, 34] |
| *Actr13E* | ARP6 | ACTR6 | – | – | – | [35] |
| *Mod(mdg4)*/ *E(var)3-93D* | – | – | Transcriptional regulator, has more than 20 trans-splicing isoforms | – | – | [36] |
| *Su(var)2-10* | PIAS1 | PIAS1 | PIAS protein, JAK/STAT pathway down-regulator , E3 SUMO-ligase | – | Steroid hormones/nuclear receptors;  TGF-β/BMP/Smad; Hedgehog;  TNF-α/NF-κB. | [37-39] |
| *E(var)3-64E*/ *Ubp64Evar1* | – | – | Ubiquitin-specific protease | – | – | [40] |
| *Su(z)5* | – | – | S- adenosylmethionine synthetase | – | – | [41] |
| – | LSH (Hells) | – | Lymphocyte-specific helicase | – | – | [42] |
| **DNA-binding** | *D1* | HMGA1,  HMGA2 | HMGA1,  HMGA2 | Multi-AT-hook domain protein, minor groove binding, promotes gene repression, interacts with topoisomerase II | Diabetes, Silver-Russell syndrome. Breast, prostate, lung, pancreas, thyroid, ovarian, pituitary, gastric cancer and lipomas. | – | [33, 43, 44] |
| *mod* (*modulo*) | – | – | DNA- and RNA-binding, the phosphorylated form binds to rRNA | – | – | [45] |
| *pho* | YY1 | TYY1 | Binds 5'-CCGCCATNTT-3' and SBE -element, contribute to DNA reparation | Mental retardation syndrome. | TNF-α/NF-κB. | [46, 47] |
| *Su(var)3-7* | – |  | Zinc fingers protein binds HP1a and SU(VAR)3-9 | – | – | [48] |
| *salm*, *salr* | SALL1, -3, -4 | SALL1  SALL4 |  | Townes-Brocks syndrome (TBS)  Duane-radial ray syndrome (Okihiro Syndrome).  Acute myeloid leukemia. | Hedgehog. | [49, 50] |
| *sens*, *sens-2* | GFILb |  |  | – | – | [51] |
| *Trl* (*trithorax-like*) (*E(var)*) | – | – | GAGA- transcription factor, binds DNA repeats | – | – | [52] |
| – | IKAROS | IKAROS | Binds gamma-satellite DNA | – | Notch/Delta. | [51] |
| – | HELIOS | HELIOS | – | – | – | [53] |
| – | ZFP57 (KRAZ1) | KAP1 | DNA-binding corepressor | – | – | [54] |
| – | ZFP68 (KRAZ2) | – | – | – | – | [54] |
| – | ZFP97 (AI046551) | – | – | – | – | [33] |
| **DNA methylation** | *DMAP1* | DMAP1 | DMAP1 | DNA methyltransferase | – | – | [13] |
| *MBD-like* | MBD1, -2, -4 | MBD1 | Binds to methylated CpG, recruits SETDB1 | Autism. Prostate, lung, breast, intestine, colon, gastric cancer. | G protein–coupled receptors and  receptor tyrosine kinases  (ERK/MAPK, PI3K/AKT,  JAK/STAT, JNK, PKC);  WNT/β-catenin. | [55] |
| – | DNMT3a, DNMT3b (MommeD14) | DNMT3B | DNA methyltransferase | Immunodeficiency, centromeric region instability, facial anomalies (ICF) syndrome. Colorectal, breast cancer. | Steroid hormones/nuclear receptors; WNT/β-catenin. | [56] |
| – | DNMT1 (MommeD2) | DNMT1 | DNA methyltransferase | Schizophrenia Late onset Alzheimer’s disease (LOAD). Prostate, breast, lung, colorectal, gastric cancer, hepatocellular  carcinoma. | Steroid hormones/nuclear receptors; WNT/β-catenin. | [13] |
| – | KAISO | KAISO | – | – | WNT/β-catenin. | [57] |
| – | MBD3l1b | – | – | – | – | [58] |
| – | MECP2 | MECP2 | Binds to methylated CpG | Rett syndrome (cerebroatrophic hyperammonemia). |  | [59] |
| – | UHRF -1 | UHRF1 | – | – | – | [60] |
| – | ZBTB4 | ZBTB4 | – | – | – | [57] |
| – | ZBTB38 (CIBZ) | – | – | – | – | [61] |
| **HUSH-complex** | – | – | TASOR | – | – | – | [12] |
| – | – | MPHOSPH8 | – | – | – | [12] |
| – | – | PPHLN1 | – | – | – | [12] |
| **Replication** | *Cdc6* | CDC6 | CDC6 | – | – | Steroid hormones/nuclear receptors. | [62] |
| *Orc1* | ORC1 | ORC1 | Binds to origins of replication | – | – | [63] |
| *Orc2* | ORC2l | ORC2 | ATP-dependent subunit of the origin replication complex | – | – | [62] |
| *mus209* | PCNA | PCNA | Subunit of the origin replication complex | – | – | [64] |
| *SuUR* | – | – | Heterochromatin protein, suppressor of underreplication | – | – | [65] |
| **Chromosome segregation** | *Incenp* | INCENP | INCENP | AURKB activator, centromere component | – | – | [66] |
| **Transcription factors** | *E(var)3-93E* | E2F1 | E2F1 | E2F  transcription factor, haplo-enhancer/triplo-suppressor | – | WNT/β-catenin. | [67] |
| *slbo* | C/EBPα, C/EBPβ |  |  | – | – | [68, 69] |

**Table 2**. Diseases associated with PEV of the human genes in the result of chromosome rearrangements.

\* PEV is not confirmed.

“–” - no data.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Distance to the breakpoint** | | **Diseases** | **References** |
| **Upstream** | **Downstream** |
| *SOX9* | ~900 kb. | 1,3 mb. | Campomelic dysplasia,  Pierre Robin sequence \* | [70-72] |
| *POU3F4* | ~900 kb. | – | X-linked congenital deafness | [73] |
| *FKHL7* | ~1,2 mb. | – | Anterior segment dysgenesis | [74] |
| *MAF* | ~1 mb. | – | Cataract, coloboma, anterior segment dysgenesis | [75] |
| *SHH* | ~250 kb.; ~ 1 mb. | – | Preaxial polydactyly,  Holoprosencephaly \* | [76, 77] |
| *FOXL2* | ~170 kb. | – | Blepharophimosis | [78] |
| *PAX6* | – | ~150 kb. | Aniridia |  |
| *PLP1* | – | – | Spastic paraplegia type 2,  Pelizaeus–Merzbacher disease | [79, 80] |
| *NSD1* | – | – | Beckwith–Wiedemann syndrome,  Sotos syndrome | [81] |

**Table 3**. Human diseases developing as a result of PEV caused by microsatellite expansion (from [82] with modifications).

“–” - no data.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Repeat unit** | **Gene undergoing PEV** | **Disease** | **Inheritance pattern** | **Healthy range, no. of repeats** | **Symptomatic range, no. of repeats** | **References** |
| CCG/CGG | *XYLT1* | Baratela--Scott syndrome (BSS) | Autosomal recessive | 9-20 | 100-800 | [83, 84] |
| CCG/CGG | *DIP2B* | Mental retardation, associated with fragile site FRA12A | Autosomal dominant | 12-26 | >150 | [85] |
| CCG/CGG | *FMR1* | Fragile X mental retardation syndrome (Fragile X syndrome (FXS)) | X-linked dominant | 6-52 | >200 | [86-88] |
| CCG/CGG | *FMR2* | Mental retardation, X-linked, associated with fragile site FRAXE | X-linked recessive | 4-39 | >200 | [89-92] |
| CCG/CGG | *NOTCH2NLC* | Neuronal intranuclear inclusion disease (NIID) | Autosomal dominant | 13-30 | 60-959 | [93-96] |
| CAG | *PPP2R2B* | Spinocerebellar ataxia 12 (SCA12) | Autosomal dominant | 6-39 | 41-83 | [93-95] |
| GCA | *GLS* | Glutaminase deficiency (GD) | – | 8-16 | >400 | [97] |

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