Supplementary Figure Legends:

Supplementary Figure 1: Generation of the *E(z)^{A691}* transgenic flies under the UAS-promotor. A: Generation of the *E(z)^{A691}* transgenic flies: Original E(z)-cDNA construct – *pGEX-2T{E(z)cDNA e32}* was kindly gifted by Dr. Richard Jones, University of Dallas, Texas, USA. The *attB-E(z)* primers were designed to clone into the *pENTR-221* vector with the help of Gateway™ BP Clonase™ II Enzyme mix (Thermo Fischer-11789100). The variant primers were prepared, and the variant was generated with a Q5 mutagenesis (NEB- E0554S) as previously explained in (Tsang et al. 2016). After confirming via sequencing analysis*, pENTR-221-E(z)cDNA^{WT} and pENTR-221-E(z)^{A691G}* were cloned into pGW.attB vector by using Gateway™ LR Clonase™ II Enzyme mix (Thermo Fischer-11791020). Sequence-verified wild-type and variant constructs were then microinjected in VK00037 attP docking site embryos to generate *pBac{UASg-E(z)^{WT}}VK00037* and *pBac{UASg-E(z)^{A691G}}VK00037* transgenic lines. Table B: Overexpression assay: performed with different *GAL4* lines at different temperatures

Supplementary Figure 2: Generation of the human *EZH1-cDNA* transgenic flies under *UAS* promotor: Human cDNA "*IOH10021*" from the Ken Scott collection was used for these constructs. By designing the site-specific primers, the variant was generated with a Q5 mutagenesis protocol (NEB- E0554S) and after confirming via Sanger sequencing analysis, both the *pENTR-221-EZH1^{ref}* and *pENTR-221-EZH1^{A678G}* constructs were cloned into *pGW-{UASg}* vector by using LR Clonase™ II (Thermo Fischer-11791020). Sequence-verified *pattB{UAS-EZH1^{ref}}* & *pattB{UAS-EZH1^{A678G}}* constructs were microinjected into VK00033 docking site embryos to generate *pBac{UAS-EZH1^{ref}}VK00033* & *pBac{UAS-EZH1^{A678G}}VK00033*.

Supplementary Figure 3: Generation of the *E(z)^{A691}* transgenic flies under the constitutively active tubulin promotor. *pwmc{ptub:EGFP::E(z)}* construct and flies were gifted by Dr. Leonie Ringrose, IRI Life Sciences, Berlin, Germany. The wildtype construct underwent mutagenesis. The variant was generated with a Q5 mutagenesis protocol (NEB- E0554S). Both wild-type and variant constructs underwent restriction digestion with NotI (NEB- R3189S) and XbaI (NEB-R0145S) and then ligated into the pattB-Basler vector with the T4 DNA ligase (NEB M0202S). Sequenced varified *pattB{ptub:EGFP::E(z)^{WT}}*, and *pattB{ptub:EGFP::E(z)^{A691G}}* then microinjected in *ϕc31* mediated *VK00037* docking site embryos to generate *pBac{ptub:EGFP::E(z)^{WT}}VK00037* and *pBac{ptub:EGFP::E(z)^{A691G}}VK00037* transgenic flies.