**Table S1,** Summary of family members analyzed in our study including the consideration of being a carrier of the cancer-causing variant. *CRC – colorectal cancer, P - colorectal polyps*

| Classification | ID | Sex | Age at sampling | Age of onset of CRC | Age of onset of P | Considered as a carrier of the variant? |
|---|---|---|---|---|---|---|
| **Cases** | III7 | male | - | 52 x2 | | Yes |
| | III8 | female | - | 35 | - | Yes |
| **Case / possible phenocopy** | II7 | female | - | 83 | - | Yes/No |
| **Polyps** | III10 | female | | - | 56, 59, 71 | Yes/No |
| **Controls** | III3 | female | 56 | - | - | No |
| | IV3 | female | 53 | - | - | No |

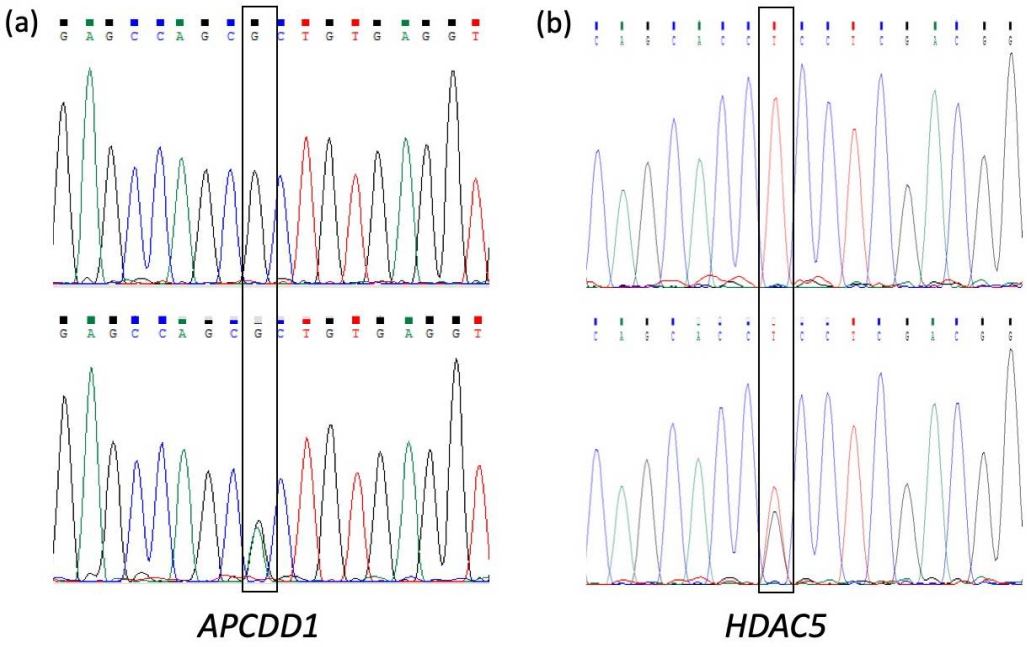


**Figure S1.** Representative electropherograms depicting the *APCDD1* and *HDAC5* variants identified in the studied CRC family. **(a)** Sanger sequencing confirmed the wild type sequence of *APCDD1* gene for family members II7, III3 and IV3 (upper panel) and the heterozygous missense variant (p.R299H) for the family members III7, III8 and III10. **(b)** Sanger sequencing confirmed the wild type sequence of *HDAC5* gene for family members III3, III10 and IV3 (upper panel) and the heterozygous 5'UTR variant (T → G) for family members II7, III7 and III8 (lower panel).

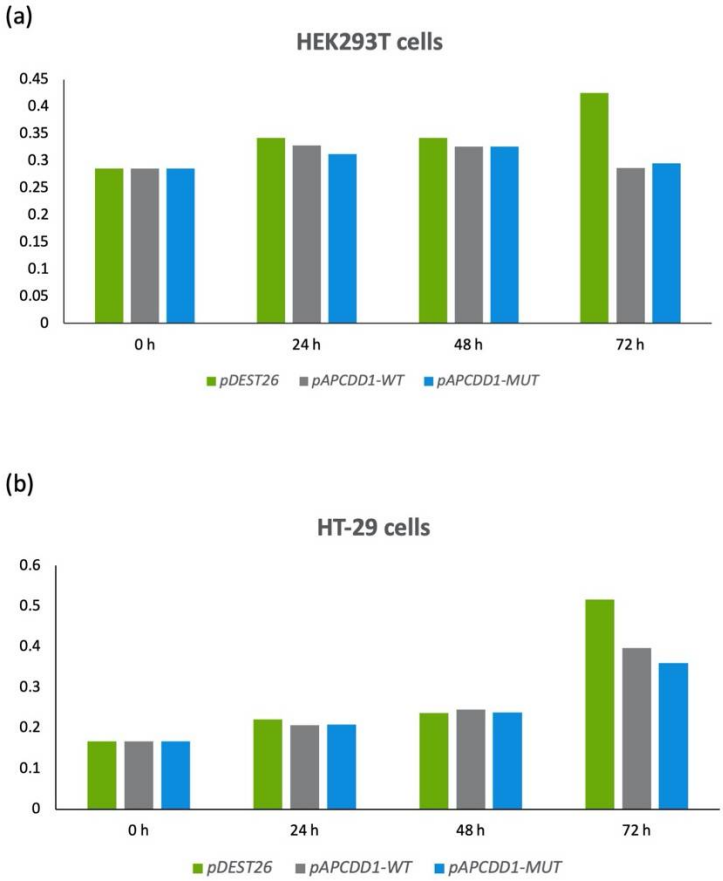


**Figure S2.** Cell proliferation assays conducted for *pAPCDD1*$^{WT}$ and *pAPCDD1*$^{MUT}$ using **(a)** HEK293T and **(b)** HT-29 cell lines. *pDEST26* vector was used as negative control. No significant increase of viable cell numbers was found between *pAPCDD1*$^{WT}$ and *pAPCDD1*$^{MUT}$ transfected cells at any measured time point ($p = 0.05$).

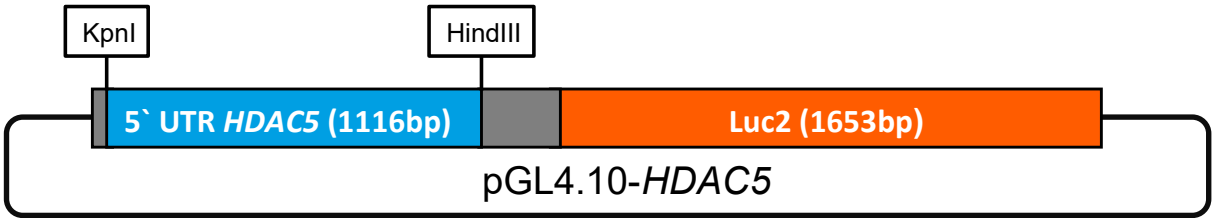


**Figure S3.** Graphical overview of pGL4.10-*HDAC5* reporter constructs. 5´UTR of *HDAC5* gene was cloned into the multiple cloning site directly upstream of the *luc2* reporter gene. Restriction sites for Kpn I and Hind III are indicated by arrows.