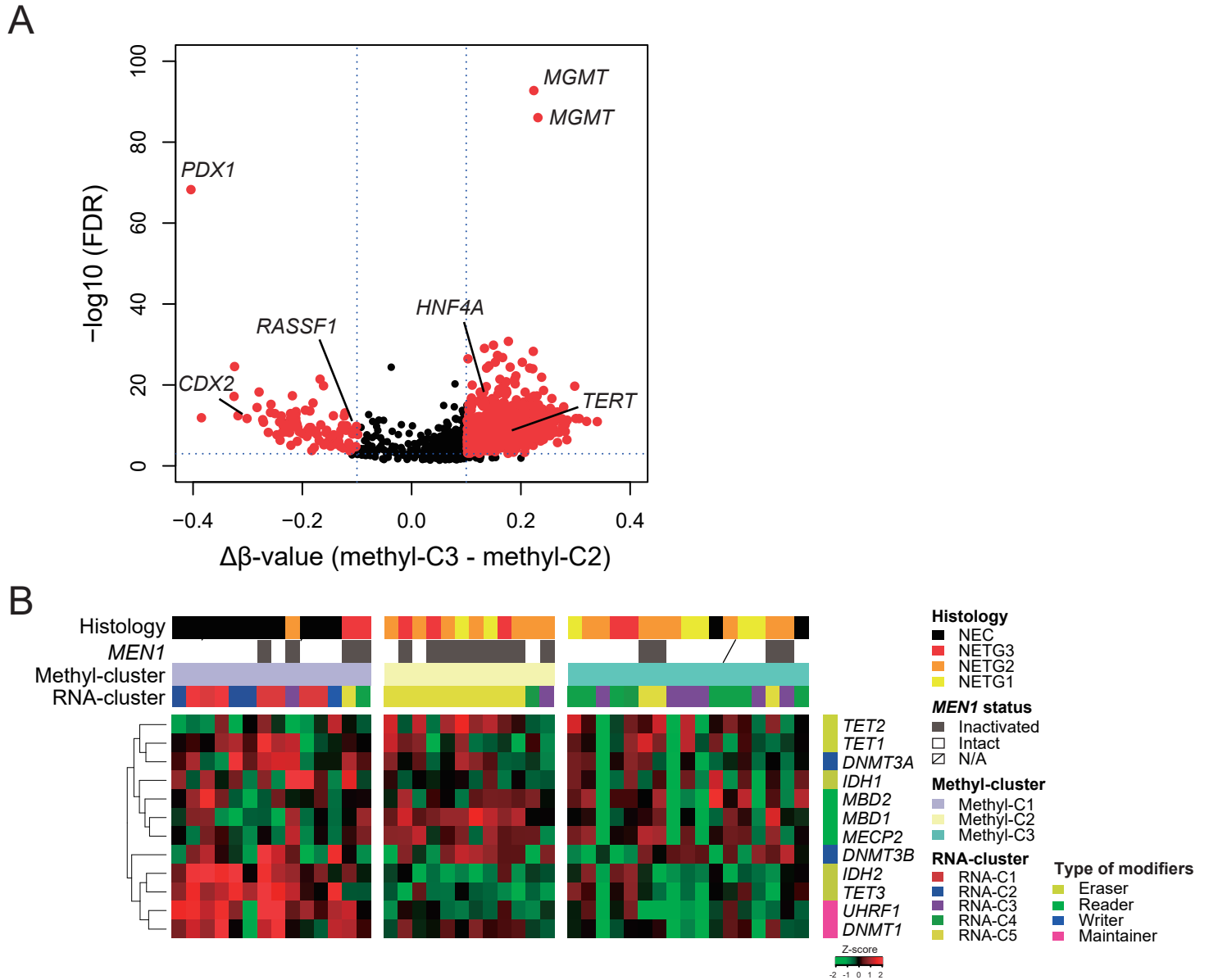


Supplementary Figure S15. DNA methylation status in Panc-NETs.



A, Volcano plot showing the differential methylation status of DMRs between the two clusters (Methyl-C2 and Methyl-C3) in Fig. 2C. Methyl-C2 shows hypermethylation of *PDX1*, *CDX2*, and *RASSF1* and hypomethylation of *HNF4A* and 18 genes listed in COSMIC Cancer Gene Census (e.g., *MGMT*, *TERT*), compared to Methyl-C3. The horizontal dot line corresponds to a FDR *P*-value of 0.05.

B, Gene expression of DNA methylation modifiers based on RNA-seq. The histology (NET/NEC), the status of *MEN1*, and clusters based on RNA-seq are indicated at the top. In the Methyl-C1 group mostly consisting of NECs, the expression of *IDH2* (versus Methyl-C2, $P = 8.00 \times 10^{-5}$; versus Methyl-C3, $P = 6.47 \times 10^{-5}$), *TET3* (versus Methyl-C2, $P = 5.16 \times 10^{-5}$; versus Methyl-C3, $P = 4.85 \times 10^{-4}$), *UHRF1* (versus Methyl-C2, $P = 5.06 \times 10^{-4}$; versus Methyl-C3, $P = 8.75 \times 10^{-5}$), and *DNMT1* (versus Methyl-C3, $P = 0.00137$) are significantly higher, compared to Methyl-C2 and/or C3. In the Methyl-C2 where most cases have alterations of *MEN1*, the expression of *TET2* (versus Methyl-C1, $P = 0.0333$) and *MBD1* (versus Methyl-C1, $P = 0.00309$; versus Methyl-C3, $P = 0.00179$) are significantly higher, compared to Methyl-C1 and/or C3.