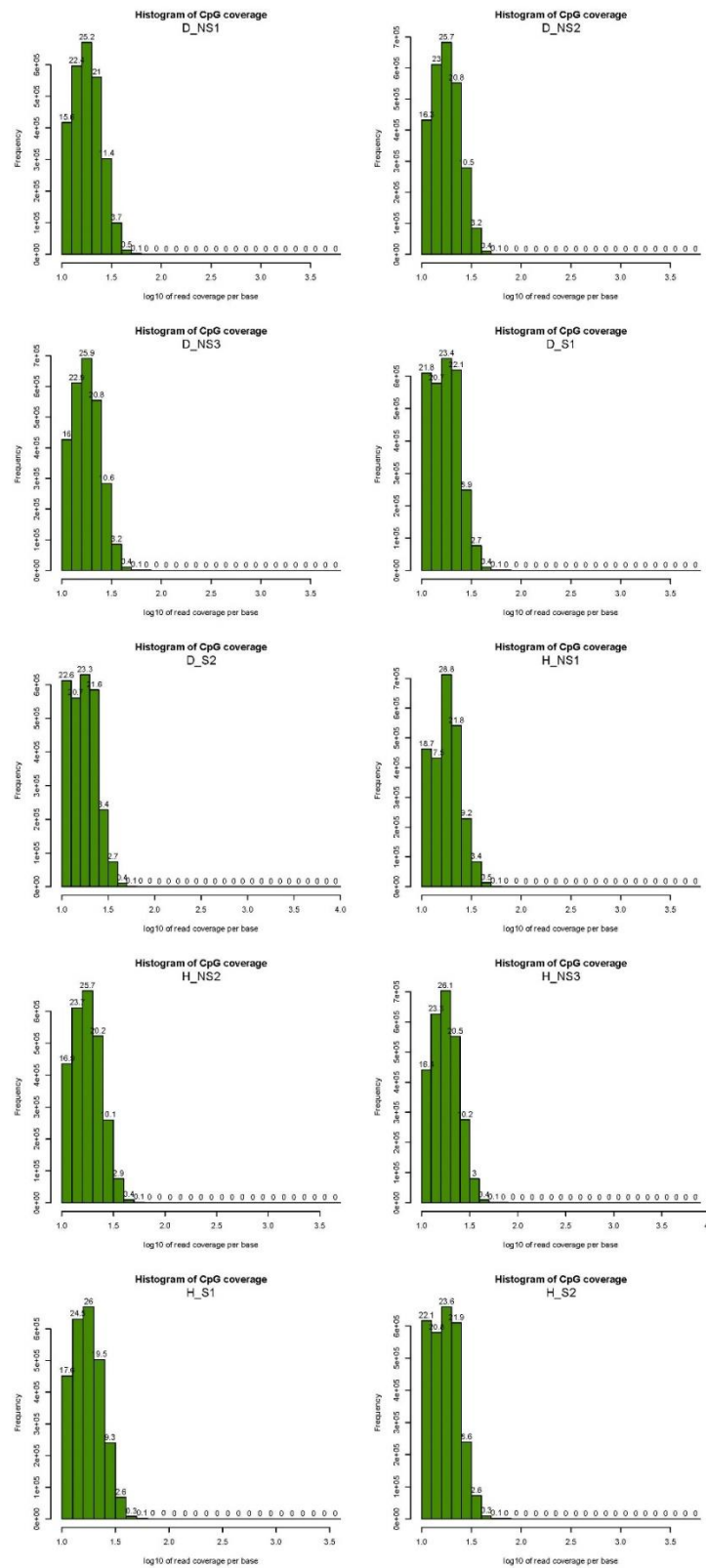
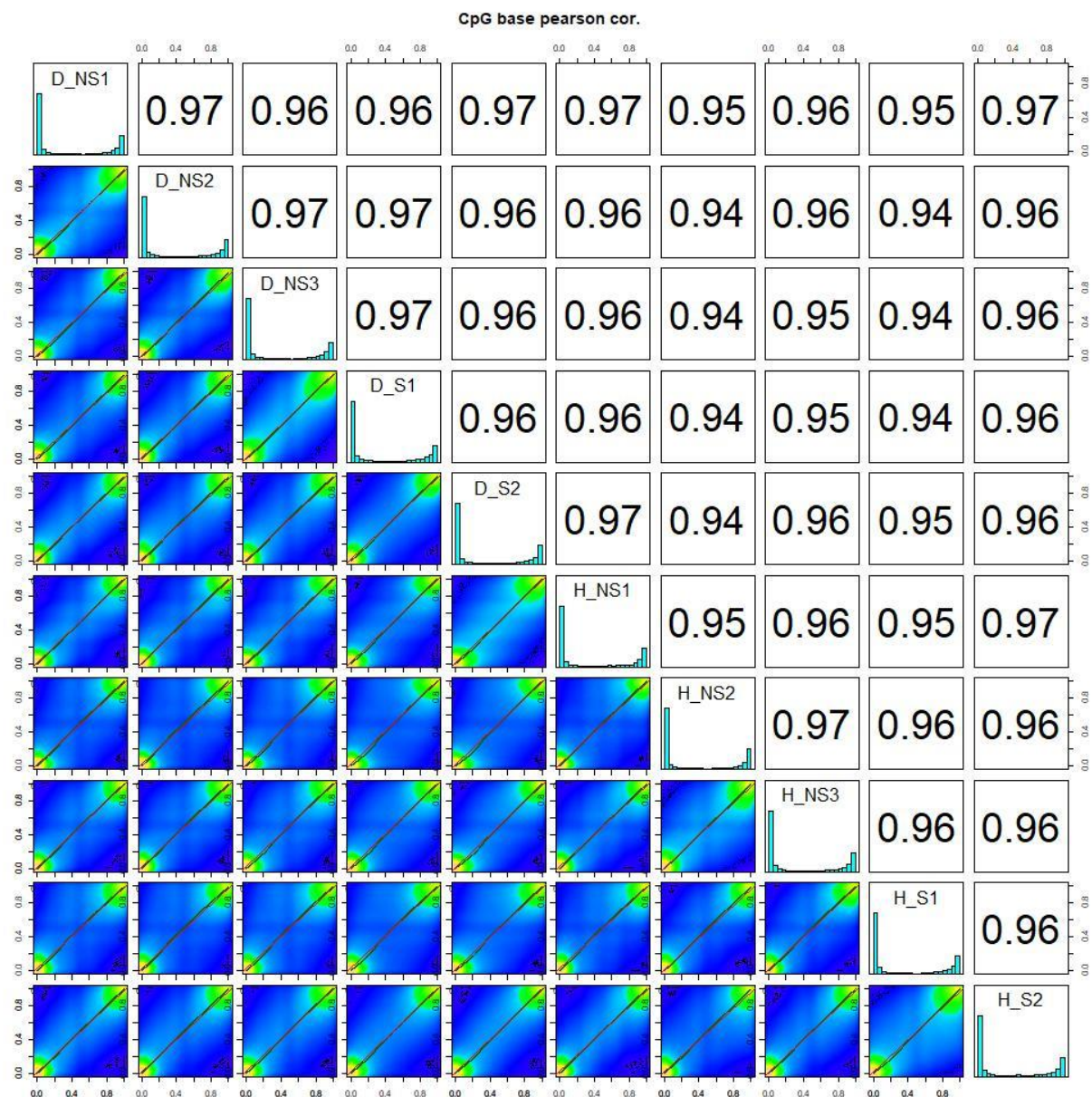


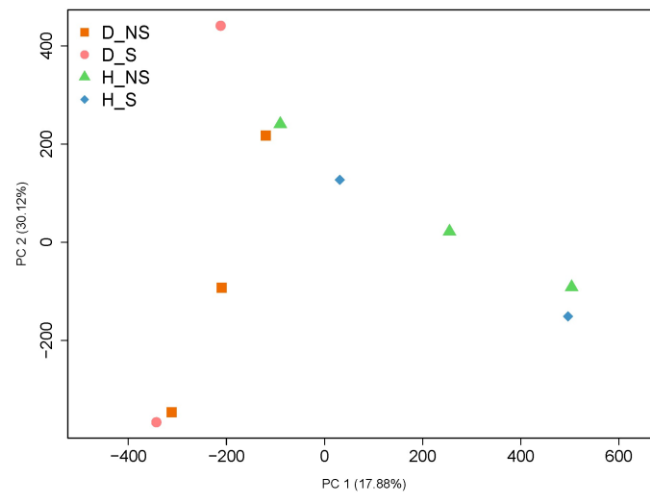
## *Supplementary Material*



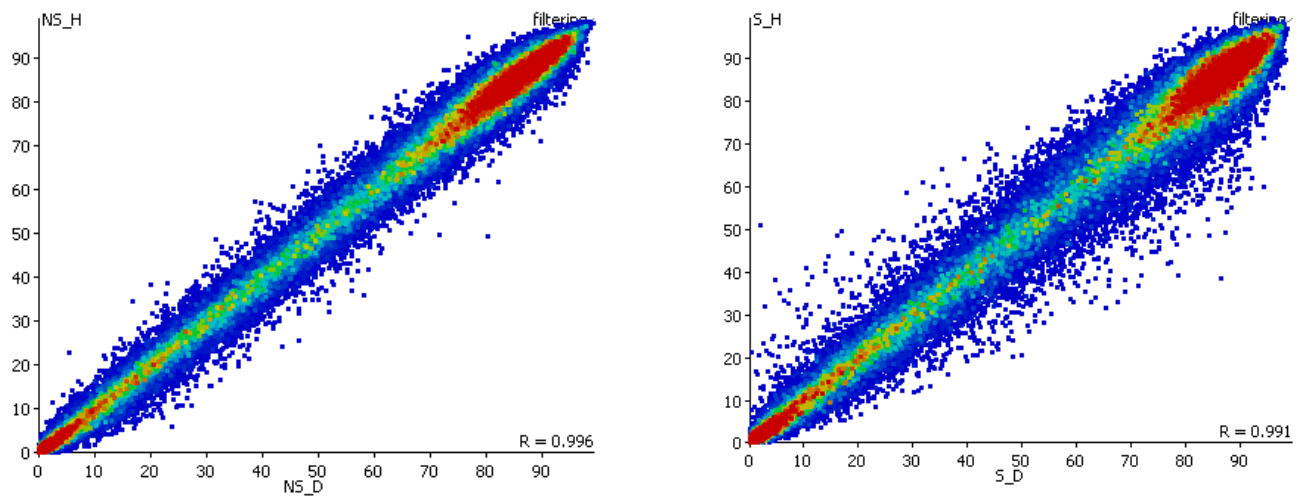
**Figure S1.** Descriptive Statistics per sample, histogram of CpG coverage of diseased non-surgical patient sample.



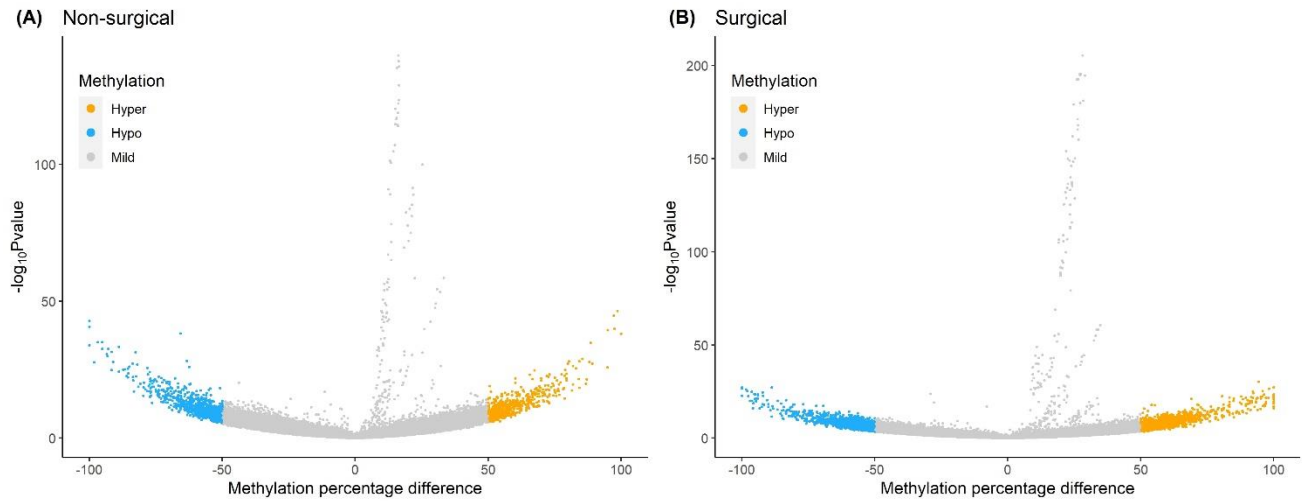
**Figure S2.** Pair-wise Pearson's correlation coefficients between different groups



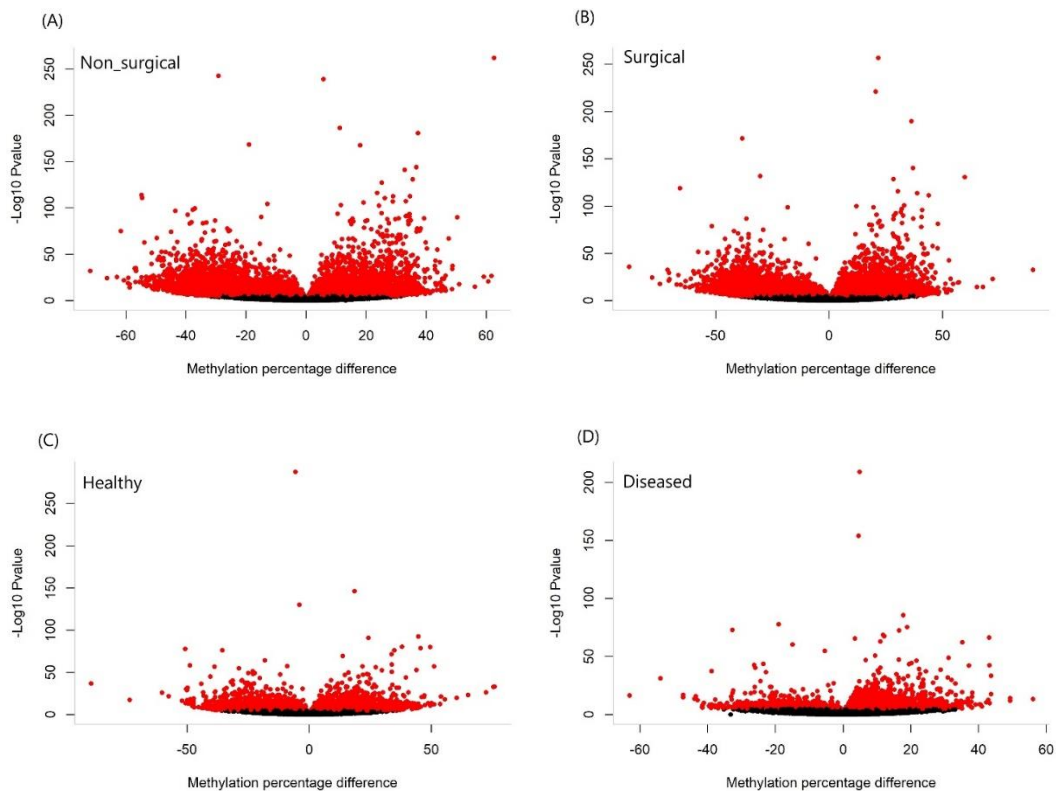
**Figure S3.** Principal Component Analysis (PCA) including all samples which demonstrates separation of the diseased and healthy samples.



**Figure S4** Scatter plots shown the correlation between healthy and diseased tissue in surgical and non-surgical group and the variation between the surgical replicates.

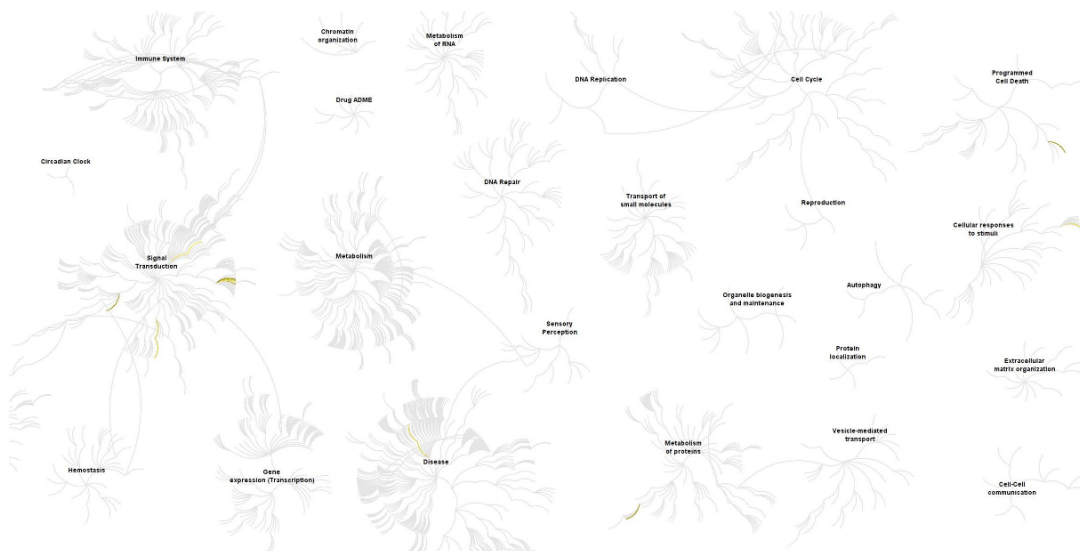


**Figure S5** Volcano plots show the mean difference between diseased and healthy patient samples in non-surgical and surgical cohorts. Yellow dots represent the hypermethylated bases, and the blue dots represent the hypomethylated bases.



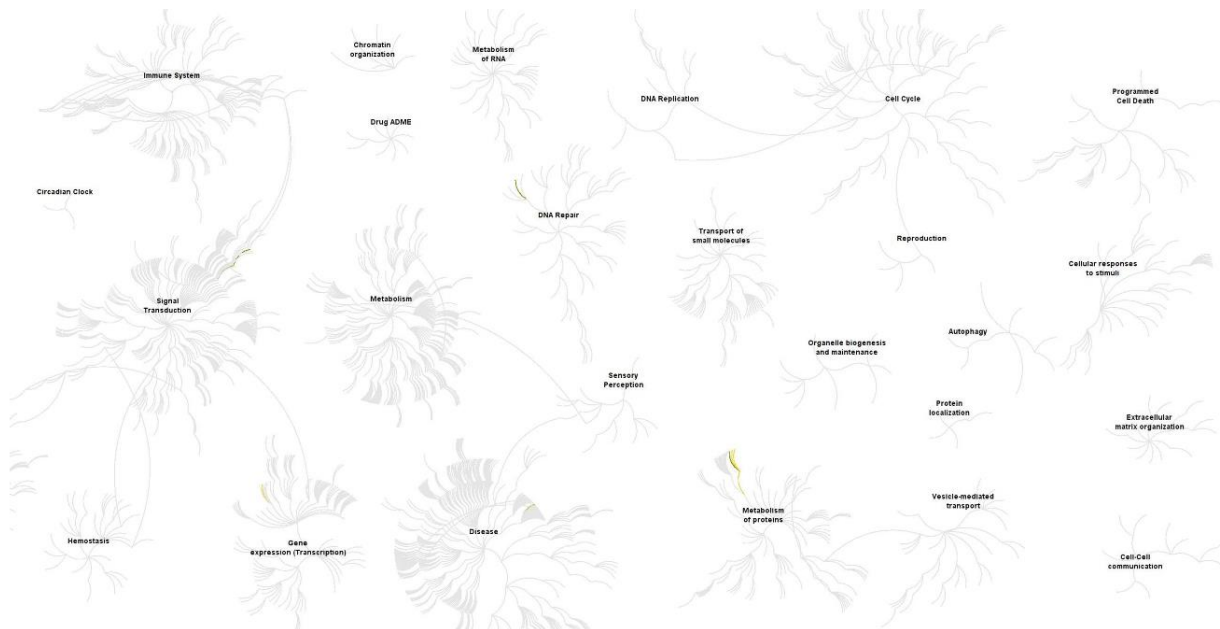
**Figure S6** (A) & (B) Volcano plots show the mean difference between diseased and healthy patient samples in non-surgical and surgical cohorts. (C) & (D) show the mean difference between non-surgical patient samples and surgical patient samples in healthy and diseased.

A



Pathway identifier	Pathway name	#Entities found	#Entities total	Entities ratio	Entities pValue	Entities FDR	#Reactions found	#Reactions total	Reactions ratio
R-HSA-186797	Signaling by PDGF	4	70	0.004558	1.06E-04	0.024959	24	31	0.002141
R-HSA-186763	Downstream signal transduction	3	37	0.002409	2.99E-04	0.035327	15	16	0.001105
R-HSA-9818030	NFE2L2 regulating tumorigenic genes	2	17	0.001107	0.001626374	0.126857	2	12	8.29E-04
R-HSA-9013026	RHOB GTPase cycle	3	75	0.004884	0.002273867	0.134158	3	6	4.14E-04
R-HSA-2219530	Constitutive Signaling by Aberrant PI3K in Cancer	3	96	0.006251	0.004532583	0.201327	1	2	1.38E-04
R-HSA-2219528	PI3K/AKT Signaling in Cancer	3	124	0.008074	0.009130356	0.201327	1	21	0.00145
R-HSA-6811558	PI3P, PP2A and IER3 Regulate PI3K/AKT Signaling	3	129	0.0084	0.010157082	0.201327	1	7	4.83E-04
R-HSA-199418	Negative regulation of the PI3K/AKT network	3	137	0.008921	0.011934714	0.201327	1	10	6.91E-04
R-HSA-8980692	RHOA GTPase cycle	3	154	0.010028	0.016274166	0.201327	3	6	4.14E-04
R-HSA-9013106	RHOA GTPase cycle	2	79	0.005144	0.03066401	0.201327	2	6	4.14E-04
R-HSA-72731	Recycling of eIF2-GDP	1	10	6.51E-04	0.03934064	0.201327	2	2	1.38E-04
R-HSA-416482	G alpha (12/13) signalling events	2	86	0.0056	0.035790828	0.201327	5	15	0.001036
R-HSA-351906	Apoptotic cleavage of cell adhesion proteins	1	11	7.16E-04	0.037264672	0.201327	1	10	6.91E-04
R-HSA-198203	PI3K/AKT activation	1	13	8.47E-04	0.043892127	0.201327	2	5	3.45E-04
R-HSA-9013423	RAC3 GTPase cycle	2	100	0.006512	0.046947174	0.201327	2	6	4.14E-04

B



Pathway identifier	Pathway name	#Entities found	#Entities total	Entities ratio	Entities pValue	Entities FDR	#Reactions found	#Reactions total	Reactions ratio
R-HSA-3065679	SUMO is proteolytically processed	2	6	3.91E-04	8.74E-04	0.289361907	2	3	2.07E-04
R-HSA-3065676	SUMO is conjugated to E1 (UBA2:SAE1)	2	8	5.21E-04	0.001539159	0.289361907	2	3	2.07E-04
R-HSA-9022707	MECP2 regulates transcription factors	2	10	6.51E-04	0.002382804	0.2978950524	2	8	5.52E-04
R-HSA-3215018	Processing and activation of SUMO	2	13	8.47E-04	0.003971554	0.373326048	5	9	6.21E-04
R-HSA-5619048	Defective SLC11A2 causes hypochromic microcytic anemia, with iron overload 1 (AHMID1)	1	3	1.95E-04	0.021070157	0.387892662	1	1	6.91E-05
R-HSA-9025046	NTF3 activates NTRK2 (TRKB) signaling	1	4	2.60E-04	0.02799532	0.387892662	3	3	2.07E-04
R-HSA-9024909	BDNF activates NTRK2 (TRKB) signaling	1	4	2.60E-04	0.02799532	0.387892662	3	3	2.07E-04
R-HSA-9026357	NTF4 activates NTRK2 (TRKB) signaling	1	4	2.60E-04	0.02799532	0.387892662	3	3	2.07E-04
R-HSA-9026527	Activated NTRK2 signals through PLCG1	1	6	3.91E-04	0.041700351	0.387892662	3	3	2.07E-04
R-HSA-5696395	Formation of Incision Complex in GG-NER	2	47	0.003060494	0.044442457	0.387892662	2	10	6.91E-04
R-HSA-9032759	NTRK2 activates RAC1	1	7	4.56E-04	0.048480892	0.387892662	2	2	1.38E-04
R-HSA-3065678	SUMO is transferred from E1 to E2 (UBE2I, UBC9)	1	7	4.56E-04	0.048480892	0.387892662	1	3	2.07E-04

**Figure S7** Reactome Pathway Analysis of differentially methylated genes in Non-Surgical (A) and Surgical (B) Groups. Overrepresented pathways are depicted by gold lines in the analysis. The tables showcase details of the top pathways with a p-value < 0.05.