

## Distinct features between *MLH1*-methylated and unmethylated colorectal carcinomas with the CpG island methylator phenotype: implications in the serrated neoplasia pathway

### Supplementary Material

**Supplementary Table S1.** Comparison of the frequency of mucinous differentiation between *MLH1*-methylated and unmethylated tumors in proximal-located CIMP-H colon carcinomas (original study cohort; n = 45)

		Case No.	<i>MLH1</i> -methylated (n = 27)	<i>MLH1</i> -unmethylated (n = 18)	<i>P</i> -value
Mucinous histology	Absent	22	8 (30%)	14 (78%)	0.002
	Present	23	19 (70%)	4 (22%)	

**Supplementary Table S2.** Comparison of the frequency of mucinous differentiation between *MLH1*-methylated and unmethylated tumors in distal-located CIMP-H CRCs (original study cohort; n = 20)

		Case No.	<i>MLH1</i> -methylated (n = 6)	<i>MLH1</i> -unmethylated (n = 14)	<i>P</i> -value
Mucinous histology	Absent	12	1 (17%)	11 (79%)	0.018
	Present	8	5 (83%)	3 (21%)	

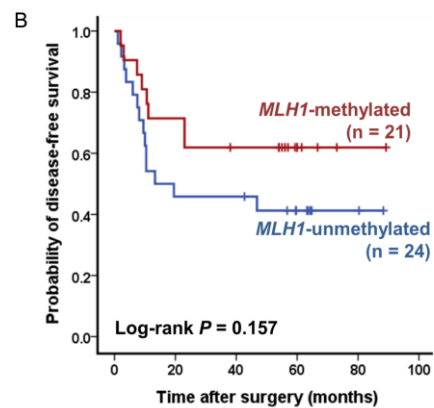
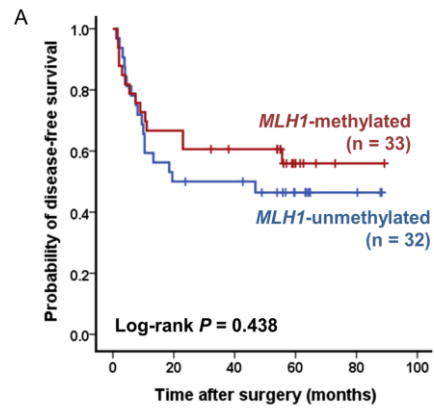
**Supplementary Table S3.** Comparison of the frequency of mucinous differentiation between MSI-H and MSS/MSI-L tumors in CIMP-L/0

CRCs (independent cohort; n = 687)

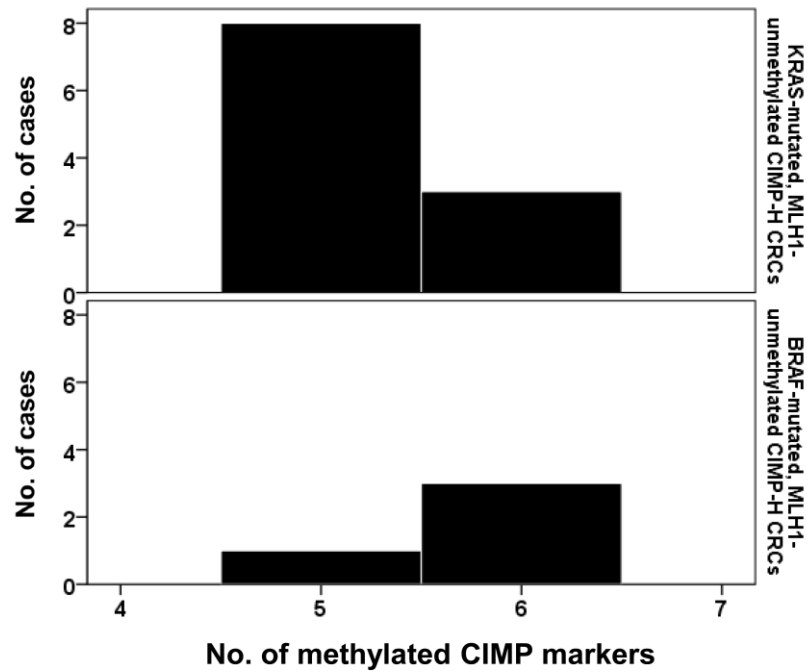
		Case No.	MSI-H, CIMP-L/0 (n = 47)	MSS/MSI-L, CIMP-L/0 (n = 640)	P-value
Mucinous histology	Absent	613	30 (64%)	583 (91%)	< 0.001
	Present	74	17 (36%)	57 (9%)	

**Supplementary Table S4.** Clinicopathologic features of *BRAF*-mutated, *MLH1*-unmethylated CIMP-H CRCs (original study cohort; n = 4)

Case #	Age	Sex	Tumor location	TNM stage	Tumor differentiation	Lymphatic invasion	Venous invasion	Perineural invasion	Tumor budding	MSI status	Death or tumor recurrence	Disease-free survival
SD-074	52	Female	Ascending colon	Stage IV (pT4N2M1)	Poorly differentiated	Present	Present	Present	Present	MSS	Yes (death)	3.2 months
SD-226	49	Female	Rectum	Stage IV (pT4N1M1)	Poorly differentiated	Present	Absent	Present	Present	MSS	Yes (death)	3.8 months
SD-461	52	Female	Ascending colon	Stage II (pT3N0M0)	Moderately differentiated	Absent	Absent	Present	Present	MSS	No	42.7 months
SD-733	49	Female	Transverse colon	Stage III (pT3N2M0)	Moderately differentiated	Present	Absent	Present	Present	MSS	Yes (recurrence)	19.5 months



**Supplementary Figure S1.** Kaplan-Meier survival analysis with log-rank test. **(A)** Survival analysis in 65 CIMP-H CRCs. **(B)** Survival analysis in 45 CIMP-H CRCs treated with 5-FU-based adjuvant chemotherapy.



**Supplementary Figure S2.** Comparison of number of methylated CIMP markers between *KRAS*-mutated and *BRAF*-mutated tumors in *MLH1*-unmethylated CIMP-H CRCs (n = 15).