Effect of site-specific methylation on DNA modification methyltransferases and restriction endonucleases

Michael Nelson and Michael McClelland*

Department of Biochemistry and Molecular Biology, University of Chicago, 920 East 58th St., Chicago, IL 60637, USA

INTRODUCTION

We present in **Table I** an updated list of the sensitivities of 194 restriction endonucleases to the site-specific DNA modifications: ^{m4}C, ^{m5}C, ^{hm5}C, and ^{m6}A (M13,M15,M18,M20,N7). These four modifications are found commonly in DNA of prokaryotes, eukaryotes, and their viruses.

Table II is a list of 117 characterized DNA methyltransferases. The cloning of Type I and II restriction modification genes has been reviewed recently by Wilson (W17).

Many DNA methyltransferases are sensitive to non-canonical modifications within their recognition sequences (B36,M19a,N7,P13), and this sensitivity may differ from that of their restriction endonuclease partners. **Table III** lists the sensitivities of 22 Type II DNA methyltransferases to ^{m4}C, ^{m5}C, ^{hm5}C, and ^{m6}A modification.

Several restriction endonuclease isoschizomers are known to differ in their sensitivity to methylation at particular modified sites. **Table IV** lists fifteen known isoschizomer pairs and the modified restriction sites at which they differ. Such pairs allow the assay of methylation in genomic DNAs by restriction cleavage.

Effect of ^{m5}CG and ^{m5}CNG on restriction endonucleases

Enzymes that are *not* sensitive to site-specific methylation are particularly useful for achieving complete digestion of methylated DNA. For instance, endonucleases that are unaffected by ^{m5}CG and ^{m5}CNG are useful for digestion of plant DNA which is methylated at these positions. Endonucleases that are unaffected by these two cytosine modifications include: AccIII, AflII, AhaIII, AseI, AsuII, BclI, BspHI, BspNI, BstEII, BstNI, CviQI, DpnI, DraI, EcoRV, HinCII, HpaI, KpnI, MboII, MseI, NdeI, NdeII, RsaI, RspXI, SfiI, SpeI, SphI, SspI, TaqI, TthHBI and XmnI.

CpG sequences are particularly rare and often methylated in mammalian genomes (M19). Almost all the enzymes that could generate large fragments of mammalian DNA are blocked by this ^{m5}CpG modification, including; BssHII, BspMII, ClaI, CspI, EagI, Eco47III, FspI, MluI, NaeI, NarI, NotI, PvuI, RsrII, SalI, XhoI and XorII (see **Table I**). Of enzymes with CpG in their recognition sequence, only AccIII, AsuII, Cfr9I and XmaI

are known to cut ^{m5}CG-modified DNA and will cut to completion at all of their restriction sites in mammalian DNA.

Rate of cleavage at methylated restriction sites

^{m4}C, ^{m5}C, ^{hm5}C, and ^{m6}A are bulky alkyl substitutions in the major groove of B-form DNA. It is therefore not surprising that certain site-specific DNA methylations will block many sequence-specific DNA binding proteins (S21,W10) including restriction endonucleases and DNA methyltransferases. Canonical site-specific methylation always inhibits DNA cleavage by a restriction endonuclease. Methylation at overlapping non-canonical sites inhibits the rate of duplex DNA cleavage at least ten-fold in about half of the cases tested (**Table I**). In other cases, non-canonical methylation has no effect on restriction cleavage. There are, however, a few examples in which non-canonical methylation slows cleavage by only a few fold or permits nicking of one strand of a hemi-methylated duplex. These cases are presented in footnotes to **Table I**.

Effect of site-specific methylation on DNA methyltransferases

Twenty-two Type II methyltransferases which have been tested for sensitivity to *non-canonical* DNA modifications, of which nine were blocked**Table III** (M19a).

Just as rate effects are sometimes seen with restriction endonuclease acting at certain modified sequences, rate effects are seen with DNA methyltransferases methylating non-canonically modified sequences. For example, *E. coli* Dam methyltransferase is unaffected by GAT^{m4}C, but methylates GAT^{m5}C relatively slowly. Such data is summarized in **Table III** and the footnotes to **Table I**.

Methylase/endonuclease combinations can produce novel DNA cleavage specificities

Three different strategies involving combinations of modification methyltransferases and restriction endonucleases have been used to generate rare or novel DNA cleavage sites.

First, certain adenine methyltransferases may be used in conjunction with the methylation-dependent restriction endonuclease DpnI to create cleavages at defined eight to twelve base pair sequences (M16,M21). M·ClaI and DpnI have been used to cut the 2.8 million base pair *Staphylococcus aureus* genome into two pieces (W11).

Second, protection of a subset of restriction endonuclease cleavage sites by methylation at overlapping methyltransferase/endonuclease targets has been described (K14,N6,N9). This two-step "cross-protection" strategy has produced over 60 new cleavage specificities, and many more are possible (J1,K1,K14,N9).

Finally, methyltransferases may be used to block modification by other methyltransferases. Blocking a subset of DNA methyltransferase sites by overlapping methylation (sequential double-methylation) can expose a subset of restriction endonuclease sites for cleavage (M19,N7,P12). For instance, M·HpaII, M·BamHI, and BamHI have

been used in a sequential three-step methyltransferase/methyltransferase/endonuclease reaction to achieve selective DNA cleavage at the ten base pair sequence, CCGGATCCGG (M19a).

Methylation-dependent restriction systems in bacteria

E. coli K-12 contains at least three different methylation-dependent restriction systems which distinguish various methylated target sequences: mrr (^{m6}A), mcrA (^{m5}CG), mcr B (R^{m5}C) (B28,H3,R1,R2). *In vivo* or *in vitro* modified DNA is inefficiently cloned into *E. coli*. For example, human DNA which is extensively methylated at ^{m5}CpG is restricted by mcrA (W18). Appropriate non-restricting strains of *E. coli* (G9,R1,R2) should be chosen for efficient transformation and cloning of methylated DNA.

TABLE I: Methylation sensitivity of restriction endonucleases [a]

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
AacI	CCWGG	C^{m5}CWGG	?	B31
AatI	AGGCCT	?	AGG^{m5}CCT AGGC^{m5}CT	S20,S20
AccI	GTMKAC	?	GTMK^{m6}AC# GTMKA^{m5}C	L15,M12
AccII	CGCG	?	^{m5}CGCG	G2
AccIII	TCCGGA	T^{m5}CCGGA TC^{m5}CGGA	TCCGG^{m6}A	K8,S4
AflI	GGWCC	GGWC^{m5}C	?	M20,W13
AhaII	GRCGYC [b]	?	GR^{m5}CGYC GRCGY^{m5}C	K1,N6
AluI	AGCT	?	^{m6}AGCT AG^{m4}CT	G15,M20,N6
			AG^{m5}CT#	H9
			AG^{hm5}CT	B36
AlwI	GGATC	?	GG^{m6}ATC GGAT^{m4}C	N5
AmaI	TCGCGA	TCGCG^{m6}A	?	M22
AosII	GRCGYC	?	GR^{m5}CGYC	E2,G15,V2
ApaI	GGGCCC	?	GGG^{m5}CCC# GGGCC^{m5}C	L5,T1
ApaLI	GTGCAC	GTGC^{m6}AC	?	H7
ApyI	CCWGG	C^{m5}CWGG [b]	^{m5}CCWGG	D4,K14,M20,R3,R8
AquI	CYCGRG	?	^{m5}CYCGRG#	K5
Asp718I	GGTACC	GGT^{m6}ACC [b]	GGTAC^{m5}C GGTA^{m5}C^{m5}C [b]	M27,N5
AsuII	TTCGAA	TT^{m5}CGAA	?	G16
AtuCI	TGATCA	?	TG^{m6}ATCA	R8,S9
AvaI	CYCGRG	C^{m6}CCGGG	^{m5}CYCGR CY^{m5}CGRG	B17,E2,J12, K3,K5,M20
			CTCG^{m6}AG [b]	N6
AvaII	GGWCC	?	GGW^{m5}CC	B3,K16,M6,

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
			GGWC^{m5}C	M19a,M20
			GGW^{hm5}C^{hm5}C	H9
BalI	TGGCCA	?	TGG^{m5}CCA$^{\#}$	G6,T1
			TGGC^{m5}CA [b]	
BamHI	GGATCC	GGATC^{m5}C	GGAT^{m4}CC$^{\#}$	B31,D7,H1,H9
		GG^{m6}ATCC	GGAT^{m5}CC	L4,M5
		GG^{m6}ATC^{m5}C	GGAT^{hm5}C^{hm5}C	
BamFI	GGATCC	GG^{m6}ATCC	?	A1
BamKI	GGATCC	GG^{m6}ATCC	?	A1
BanI	GGYRCC [b]	GG^{m5}CGCC	?	K1
BanII	GRGCYC	?	GRG^{m5}CYC	N6,N9
BanIII	ATCGAT	?	ATCG^{m6}AT	S25
BbvI	GCWGC	?	G^{m5}CWGC$^{\#}$	D5,H1,V7
BclI	TGATCA [b]	TGAT^{m5}CA	TG^{m6}ATCA	B3,B15,B31,E3,R8
			TGAT^{hm5}CA	H9
BcnI	CCSGG	^{m5}CCSGG	C^{m4}CSGG$^{\#}$	J6,J7,K14
BepI	CGCG	?	^{m5}CGCG	K9
BglI	GCCN$_5$GGC	GC^{m5}CN$_5$GGC	G^{m5}CCN$_5$GGC	K14,K16,N6,M20
			GCCN$_5$GG^{m5}C [b]	
BglII	AGATCT [b]	AG^{m6}ATCT	AGAT^{m5}CT	B15,B31,D7,D9,E3,
			AGAT^{hm5}CT	H9,P8
BinI	GGATC	?	GG^{m6}ATC	B20
Bme216I	GGWCC	?	GGWC^{m5}C	M9
Bsp1286I	GDGCHC	?	GDG^{m5}CHC	N6,N9
BspHI	TCATGA	?	TCATG^{m6}A	M11
BspMI	ACCTGC	?	ACCTG^{m5}C	M20
BspMII	TCCGGA	TCCGG^{m6}A	T^{m5}CCGGA	S4
			TC^{m5}CGGA	
BspNI	CCWGG	^{m5}CCWGG	?	N5
		C^{m5}CWGG		
BstYI	RGATCY	RG^{m6}ATCY	RGAT^{m4}CY	N5
BspXI	ATCGAT	?	ATCG^{m6}AT	Z1
BspXII	TGATCA	?	TG^{m6}ATCA	Z1
BssHII	GCGCGC [b]	?	G^{m5}CG^{m5}CGC	N5
BstI	GGATCC	GG^{m6}ATCC	GGAT^{m4}CC	N5
		GGATC^{m6}C	GGAT^{m5}CC	C5
BstBI	TTCGAA	?	TTCG^{m6}AA	N5
BstEII	GGTNACC	GGTNA^{m5}C^{m5}C [b]	GGTNA^{hm5}C^{hm5}C	H9,M20
BstEIII	GATC [b]	?	G^{m6}ATC	M28,R8
BstGI	TGATCA	?	TG^{m5}ATCA	R8
BstNI	CCWGG [b]	^{m5}CCWGG [b]	^{hm5}C^{hm5}CWGG	G15,H9,M20,R8
		C^{m5}CWGG		
		^{m5}C^{m5}CWGG [b]		
BstUI	CGCG	?	^{m5}CG^{m5}CG	N8
BstXI	CCAN$_6$TGG	?	^{m5}CCAN$_6$TGG	N6
			CC^{m6}AN$_6$TGG	

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
BsuEI	CGCG	?	^{m5}CGCG#	G1,S23,S10
BsuFI	CCGG	?	^{m5}CCGG#	J12
BsuMI	CTCGAG	?	CT^{m5}CGAG#	J12
BsuQI	CCGG	?	^{m}CCGG	J11
BsuRI	GGCC	?	GG^{m5}CC# [b]	G17,K10,K11
BsuRII	CTCGAG		CT^{m}CGAG#	N17
CfoI	GCGC	?	G^{m5}CGC	E1
			G^{hm5}CG^{hm5}C	H9
CfrI	YGGCCR	?	YGG^{m5}CCR#	K14
Cfr6I	CAGCTG	?	CAG^{m4}CTG#	B36
			CAG^{m5}CTG	
Cfr9I	CCCGGG [b]	C^{m5}CCGGG	^{m4}CCCGGG	B37
		CC^{m5}CGGG	^{m5}CCCGGG	
			C^{m4}CCGGG#	
			CC^{m4}CGGG	
Cfr10I	RCCGGY	?	R^{m5}CCGGY#	B18,K14
Cfr13I	GGNCC	?	GGN^{m5}CC#	B18,K14
ClaI	ATCGAT	?	^{m6}ATCGAT	M20,M21,N5,
			AT^{m5}CGAT	
			ATCG^{m6}AT#	M12
CpeI	TGATCA	?	TG^{m6}ATCA	F3,R8
CspI	CGGWCCG	?	CGGW^{m5}CCG	M20
			^{m5}CGGWC^{m5}CG	
Csp45I	TTCGAA	?	TTCG^{m6}AA	N5
CviAI	GATC	?	G^{m6}ATC	X3
CviBI	GANTC	?	G^{m6}ANTC#	X2,X6
CviJI	RGCY	?	RG^{m5}CY#	V3,X1
CviNYI	CC	C^{m5}C	^{m5}CC#	X5
CviQI	GTAC	GTA^{m5}C	GT^{m6}AC#	X1,X4
DdeI	CTNAG	?	^{m5}CTNAG#	H8,N6
			^{hm5}CTNAG	H9
DpnI	G^{m6}ATC [b]	G^{m6}ATC	GATC	L1,M20,V11,
		G^{m6}AT^{m5}C [b]	GAT^{m4}C	N5
		G^{m6}AT^{m4}C	GAT^{m5}C	N8
DpnII	GATC	?	G^{m6}ATC#	L1,L2,L3,M7,V11
DraII	RGGNCCY	?	RGGNC^{m5}CY	S7
EaeI	YGGCCR	?	YGG^{m5}CCR#	J1,W12
			YGGC^{m5}CR	
EagI	CGGCCG	?	CGG^{m5}CCG	M20
			^{m5}CGGC^{m5}CG	
EarI	GAAGAG	?	GAAG^{m6}AG	N5
Eco47I	GGWCC	?	GGWC^{m5}C	J5
Eco47III	AGCGCT	?	AG^{m5}CGCT	N5
EcoA	GAGN$_7$GTCA [b]	?	G^{m6}AGN$_7$G^{m}TCA# [b]	B13
EcoB	TGAN$_8$TGCT [b]	?	TG^{m6}AN$_8$^{m}TGCT # [b]	B13,L6,L7
EcoDXXI	TCAN$_7$AATC [b]	?	TCAN$_7$^{m6}AA^{m}TC # [b]	P4

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
EcoE	GAGN$_7$ATGC	?	G^{m6}AGN$_7$ATGC	C8
EcoK	AACN$_6$GTGC [b]	?	A^{m6}ACN$_6$G^{m}TGC$^{\#}$ [b]	B13,B14
EcoO109I	RGGNCCY	?	RGGNC^{m5}CY	S7
EcoPI	AGACC [b]	AGA^{hm5}C^{hm5}C	AG^{m6}ACC$^{\#}$	B1,H2,R5
EcoP15	CAGCAG [b]	?	C^{m6}AGCAG$^{\#}$	H10
EcoRI	GAATTC	GAATT^{hm5}C	G^{m6}AATTC [b]	E1,M20,N6,R13,
			GA^{m6}ATTC$^{\#}$	B25,B31,D8,
			GAATT^{m5}C	H9,K2
EcoRII	CCWGG [b]	^{m5}CCWGG	^{m4}CCWGG	G13,G14,Y1,
			C^{m4}CWGG	B35,N4,R8,S9
			C^{m5}CWGG$^{\#}$	B24,M10,M20
			CC^{m6}AGG	B34
			^{hm5}C^{hm5}CWGG	H9,K2
EcoRV	GATATC	GATAT^{m5}C [b]	G^{m6}ATATC$^{\#}$	M20,N6
EcoR124	GAAN$_6$RTCG [b]	?	GA^{m6}AN$_6$RTCG	P16
			GAAN$_6$R^{m}TCG	B12
EcoR124/3	GAAN$_7$RTCG [b]	?	^{m6}A	P15.
EspI	GCTNAGC	GCTNAG^{m5}C	G^{m5}CTNAGC	N5
Fnu4HI	GCNGC	?	G^{m5}CNGC	K16,T1
			GCNG^{m5}C	
FnuDII	CGCG	?	^{m5}CGCG	G1,G2,N6,N9,S24
			CG^{m5}CG	
FnuEI	GATC	G^{m6}ATC [b]	?	L14,N6
FokI	CATCC	CAT^{m5}CC	GG^{m6}ATG	P12,P13,S4
		CATC^{m5}C [b]	C^{m6}ATCC	
FspI	TGCGCA	?	TG^{m5}CGCA	N5
HaeII	RGCGCY [b]	?	RG^{m5}CGCY	E2,G15,K1,K16,M20
			RG^{hm5}CG^{hm5}CY	H9
HaeIII	GGCC	GGC^{m5}C	GG^{m5}CC$^{\#}$ [b]	B3,K1,K16,M4,M5
			GG^{hm5}C^{hm5}C	H9
HapII	CCGG	?	C^{m5}CGG$^{\#}$	E2,W1
HgaI	GACGC	?	GACG^{m5}C	M20
HgiAI	GRGCYC	?	GRG^{m5}CYC	N6,W14
HgiJII	GGYRCC	?	GGYRC^{m5}C	W14
HhaI	GCGC	?	G^{m5}CGC$^{\#}$	E2,K16,M6,S17
			GCG^{m5}C	M20
			G^{hm5}CG^{hm5}C	H9
HhaII	GANTC	?	G^{m6}ANTC$^{\#}$	M4,M5
HincII	GTYRAC	GTYRA^{m5}C	GTYR^{m6}AC	G15,R12
			GTYRA^{hm5}C	H9
HindII	GTYRAC	?	GTYR^{m6}AC$^{\#}$	R12
HinfI	GANTC	GANT^{m5}C [b]	G^{m6}ANTC	N6,P2
			GANT^{hm5}C	H9
HindIII	AAGCTT	?	^{m6}AAGCTT$^{\#}$	B31,G15,R12
			AAG^{m5}CTT	N6
			AAG^{hm5}CTT	H9,K2

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
HinPI	GCGC	?	G^{m5}CGC	M20,N9
HpaI	GTTAAC	GTTAA^{m5}C	GTTA^{m6}AC$^{\#}$	B31,G15,H9,Y3
			GTTAA^{hm5}C	H9
HpaII	CCGG	?	^{m4}CCGG	B37,E2,M4,M5,
			^{m5}CCGG [b]	Q2,W7,
			C^{m4}CGG [b]	
			C^{m5}CGG$^{\#}$	
			^{hm5}C^{hm5}CGG	H9
HphI	TCACC	?	T^{m5}CACC$^{\#}$	M20,N6
			GGTG^{m6}A	B3
KpnI	GGTACC [b]	GGT^{m6}ACC	?	E3,M20,N6
		GGTA^{m5}CC		
		GGTAC^{m5}C		
		GGTA^{m5}C^{m5}C [b]		
MaeII	ACGT [b]	?	A^{m5}CGT [b]	M25
MboI	GATC [b]	GAT^{m4}C	G^{m6}ATC$^{\#}$	B28,G5,M18
		GAT^{m5}C [b]	GAT^{hm5}C	H9,M10,R8
MboII	GAAGA	T^{m5}CTT^{m5}C [b]	GAAG^{m6}A$^{\#}$	B3,M20,M21,N6,
MflI	RGATCY [b]	?	RG^{m6}ATCY	O1
			RGAT^{m4}CY	
			RGAT^{m5}CY	
MluI	ACGCGT	^{m6}ACGCGT	A^{m5}CGCGT	M20,S10,S23
MmeII	GATC	?	G^{m6}ATC	B23
MnlI	CCTC [b]	?	^{m5}CCTC	E3,M20
			^{m5}C^{m5}CT^{m5}C	
MphI	CCWGG [b]	?	C^{m5}CWGG	R8
MroI	TCCGGA	TCCGG^{m6}A	?	M11
MspI	CCGG [b]	^{m4}CCGG	^{m5}CCGG$^{\#}$	E2,J11,V2,W1,W7
		C^{m4}CGG	^{hm5}C^{hm5}CGG	B37,H9
		C^{m5}CGG		
MstII	CCTNAGG	^{m5}CCTNAGG	?	M20
MvaI	CCWGG	C^{m5}CWGG [b]	C^{m4}CWGG$^{\#}$	B35
		^{m5}CCWGG	CC^{m6}AGG	G13,G14
			^{m4}CCWGG [b]	K22
NaeI	GCCGGC [b]	?	G^{m5}CCGGC	E3,K14,M20,N8
			GC^{m5}CGGC	
			GCCGG^{m5}C	
NanII	G^{m6}ATC [b]	G^{m6}ATC	GATC	P1,N8
		G^{m6}AT^{m5}C [b]	GAT^{m5}C	
NarI	GGCGCC	GGCGC^{m5}C	GG^{m5}CGCC	K16,M20,N8
NciI	CCSGG	^{m5}CCSGG	C^{m4}CSGG	B31,D3,K16,M20
			C^{m5}CSGG [b]	
NcoI	CCATGG	?	^{m4}CCATGG [b]	K14,N6
NcrI	AGATCT	AG^{m6}ATCT [b]	?	Q1
NcuI	GAAGA	GAAG^{m6}A	?	M22

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
NdeI	CATATG	^{m5}CATATG [b]	^{m6}A	B8,M20
NdeII	GATC	GAT^{m5}C [b]	G^{m6}ATC	M19
NgoI	RGCGCY	?	RG^{m5}CGCY	K15,K16
NgoII	GGCC	?	GG^{m5}CC[#]	K15,K16
NgoBI	TCACC	?	T^{m5}CACC	P6,P7
NheI	GCTAGC	?	GCTAG^{m5}C	K14,M20,N6
NmuDI	G^{m6}ATC [b]	G^{m6}ATC	GATC	P1
NmuEI	G^{m6}ATC [b]	G^{m6}ATC	GATC	P1
NotI	GCGGCCGC	GCGGCCG^{m5}C	GCGG^{m5}CCGC	M20
			GCGGC^{m5}CGC	G1,S23
NruI	TCGCGA	?	TCGCG^{m6}A	N6
NsiI	ATGCAT	?	ATGC^{m6}AT	B9
PfaI	GATC	G^{m6}ATC [b]	?	R8,V6
PaeR7I	CTCGAG	?	CTCG^{m6}AG[#]	G8
PstI	CTGCAG	?	^{m5}CTGCAG	D5,G15,M20,N6,W2
			CTGC^{m6}AG[#]	
PvuI	CGATCG [b]	CG^{m6}ATCG	CGAT^{m4}CG	B31,B36,E3
			CGAT^{m5}CG	
PvuII	CAGCTG	?	CAG^{m4}CTG[#]	B31,B36,D5,
			CAG^{m5}CTG	E3,J6,R6
RsaI	GTAC [b]	GTA^{m5}C [b]	GT^{m6}AC	E3,N5,N8
RshI	CGATCG	CG^{m6}ATCG	?	L17
RspXI	TCATGA	?	TCATG^{m6}A	N5
RsrI	GAATTC	?	G^{m6}AATTC	M20
			GA^{m6}ATTC[#] [b]	B4
RsrII	CGGWCCG	?	CGGW^{m5}CCG	M20
			^{m5}CGGW^{m5}CG	
SacI	GAGCTC	G^{m6}AGCTC	GAG^{m5}CTC	M20
SacII	CCGCGG	?	^{m5}CCGCGG	K14,N6
SalI	GTCGAC	?	GT^{m5}CGAC	B31,E2,L15,
			GTCG^{m6}AC[#]	M12,R9,V3
SalDI	TCGCGA	TCGCG^{m6}A	?	M22
Sau3AI	GATC [b]	G^{m6}ATC	GAT^{m5}C [b]	D7,E2,J6,M12,R8
			GAT^{m4}C	N8
			GAT^{hm5}C	H9
Sau96I	GGNCC	?	GGN^{m5}CC	K16,M10,N6,P2
			GGNC^{m5}C	
			GGN^{hm5}C^{hm5}C	H9
Sbo13I	TCGCGA	TCGCG^{m6}A	?	M20
ScrFI	CCNGG	^{m5}CCNGG	C^{m5}CNGG	M20,N6
SfaNI	GATGC	GATG^{m5}C	G^{m6}ATGC	M20,P13
SfiI	GGCCN$_5$GGCC	GG^{m5}CCN$_5$GG^{m5}CC [b]	?	M20
			GGCCN$_5$GGC^{m5}C	
SflI	CTGCAG	?	CTGC^{m6}AG	B31
SinI	GGWCC	?	GGW^{m5}CC	K4
SmaI	CCCGGG	C^{m5}CCGGG	^{m4}CCCGGG	B31,B37,E2,G4

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
			^{m5}CCCGGG [b]	J6,K5,M12,Q2
			C^{m4}CCGGG [b]	
			CC^{m4}CGGG	
			CC^{m5}CGGG [b]	
SpeI	ACTAGT	?	^{m6}ACTAGT	H7
SphI	GCATGC	GCATG^{m5}C	?	M20,N6
		G^{hm5}CATG^{hm5}C		
SplI	CGTACG	CGT^{m6}ACG	?	N5
SpoI	TCGCGA	TCGCG^{m6}A	?	N5
SsoII	CCNGG	?	C^{m5}CNGG	V10
			^{m5}CCNGG	G14
Sso47I	GAATTC	?	G^{m6}AATTC#	N15
SstI	GAGCTC	?	GAG^{m5}CTC	B31,R6
			GAG^{hm5}CT^{hm5}C	H9
StuI	AGGCCT	?	AGG^{m5}CCT	C2,M20,S20
			AGGC^{m5}CT [b]	
StySBI	GAGN$_6$RTAYG [b]	?	G^{m6}AGN$_6$R^{m}TAYG# [b]	N1
StySPI	AACN$_6$GTRC [b]	?	A^{m6}ACN$_6$G^{m}TRC# [b]	N1
TaqI	TCGA	T^{m5}CGA [b]	TCG^{m6}A#	G15,H9,M12,V2
		T^{hm5}CGA [b]		H9
TaqII	GACCGA	?	G^{m6}ACCGA	N5
	CACCCA			
TaqXI	CCWGG	^{m5}CCWGG	?	G11
		C^{m5}CWGG		
TflI	TCGA	?	TCG^{m6}A	S2a,V8
ThaI	CGCG	?	^{m5}CGCG	G1
			^{hm5}CG^{hm5}CG	H9
TthHBI	TCGA	T^{m5}CGA	TCG^{m6}A#	S2a
XbaI	TCTAGA	?	TCTAG^{m6}A#	M22,W11
			T^{m5}CTAGA	G15,H9,N6
			T^{hm5}CTAGA	
XhoI	CTCGAG [b]	?	CT^{m5}CGAG	B31,E2,E3,G16,K5
			CTCG^{m6}AG	M12,V2
			^{m5}CTCGAG	
XhoII	RGATCY	RG^{m6}ATCY	RGAT^{m5}CY [b]	B31
XmaI	CCCGGG	CC^{m5}CGGG [b]	^{m4}CCCGGG	B37,Y5,Y6
			^{m5}CCCGGG	
			C^{m4}CCGGG	
			CC^{m4}CGGG	
XmaIII	CGGCCG	?	CGG^{m5}CCG	N6,T1
XmnI	GAAN$_4$TTC	GA^{m6}AN$_4$TTC	G^{m6}AAN$_4$TTC	M20,N6
			GAAN$_4$TT^{m5}C [b]	
XorII	CGATCG	CG^{m6}ATCG	CGAT^{m5}CG	B31,E2
			^{hm5}CGAT^{hm5}CG	H9

FOOTNOTES

a. # denotes canonical modification MTase specificity. M= A or C, K= G or T, N= A,C,G, or T, R= A or G, Y= C or T, W= A or T, S= G or C, D= A,G or T, H= A,C or T. Sequences are in 5'-3' order. ^{m4}C= N4-methylcytosine; ^{m5}C= C5-methylcytosine; ^{hm5}C=hydroxymethylcytosine; ^{m}C= methylcytosine, N4 or C5-methylcytosine unspecified; ^{m6}A= N6-methyladenine. Nomenclature is according to (S18) and (C6).

b.

AccI nicking occurs slowly in the unmethylated strand of the hemi-methylated sequence GTMKA^{m5}C.

AhaII (GRCGYC) will cut GRCGCC *faster* if these sites are methylated at GRCG^{m5}CC (N8), but will not cut GRCGY^{m5}C sites (N8,N6).

Asp718I cuts M·CviQI -modified (GT^{m6}AC) *Chlorella* virus NY2A DNA. Asp718I does not cut GGTAC^{m5}CWGG overlapping dcm sites (M27) or ^{m5}C-substituted phage XP12 DNA, whereas KpnI cuts XP12 readily (N5).

AvaI nicking occurs slowly in the unmethylated strand of the hemi-methylated sequence CTCG^{m6}AG/CTCGAG (N8).

BalI sites overlapping dcm sites (TGGC^{m5}CAGG) are 50-fold slower than unmethylated sites (G6).

BanI gives various rate effects when its recognition sequence is ^{m5}C-methylated at different positions (K16,P2).

BglI cleavage rate at certain hemi-methylated ^{m5}C sites varies (overlapping M·MspI - BglI and M·HpaII - BglI sites). However, ^{m5}C bi-methylated M·HaeIII - BglI sites are completely refractory to BglI (K16,N6).

BssHII does not cut M·HhaI-modified DNA, in which two different cytosine positions are hemi-methylated, G^{m5}CGCGC/GCG^{m5}CGC (N5).

M·BstI modifies the internal cytosine GGAT^{m}CC, but it is not known whether this modification is ^{m5}C or ^{m4}C (L10).

BstEII cuts the fully ^{m5}C-substituted phage XP12 DNA (N8).

BstNI cuts C^{m5}CWGG, ^{m5}CCWGG and ^{m5}C^{m5}CWGG (N8). BstNI isoschizomers that are insensitive to C^{m5}CXGG include AorI, ApyI, BspNI, MvaI and TaqXI (M14).

BsuRI nicking occurs in the unmethylated strand of the hemi-methylated sequence GG^{m5}CC/GGCC (B26,W15).

Cfr9I, see reference B37 for rate effects.

M·CreI is from the unicellular eukaryote *Chlamydomonas reinhardi* (S2).

DpnI requires adenine methylation on both DNA strands. Isoschizomers of DpnI include CfuI (G4), NanII, NmuEI, NmuDI and NsuDI (C1). DpnI cuts dam modified XP12 DNA (N9).

M·Eco dam modifies GAT^{m5}C at a reduced rate (N8). Many other bacteria that modify their DNA at G^{m6}ATC are listed in references B1 and L11.

EcoA is a Type I restriction endonuclease. ^{m}T represents a 6-methyladenine in the complementary strand.

EcoB is a Type I restriction endonuclease. ^{m}T represents a 6-methyladenine in the complementary strand.

EcoDXXI is a Type I restriction endonuclease. ^{m}T represents a 6-methyladenine in the complementary strand.

EcoK is a Type I restriction endonuclease. ^{m}T represents a 6-methyladenine in the complementary strand.

EcoPI is a Type III restriction endonuclease (B1,H2).

EcoP15 is a Type III restriction endonuclease (H10).

EcoRI cannot cut hemi-methylated G^{m6}AATTC/GAATTC sites. Bimethylated GA^{m6}ATTC/GA^{m6}ATTC sites are not cut by EcoRI or RsrI (N8). EcoRI shows a reduced rate of cleavage at hemi-methylated GAATT^{m5}C and does not cut an oligonucleotide that contains GAATT^{m5}C in both strands (B25).

EcoRII isoschizomers that are sensitive to C^{m5}CWGG include AtuBI, AtuII, BstGII, BinSI, Cfr5I, CfrII I, EclII, EcaII, Eco27I, Eco38I and MphI (R8). EcoRII shows reduced rate of cleavage at hemi-methylated ^{m5}CCWGG/CCWGG sites (Y1).

EcoRV cuts the fully ^{m5}C-substituted phage XP12 DNA (N8).

EcoR124 is a Type I restriction endonuclease. ^{m}T represents a 6-methyladenine in the complementary strand.

EcoR124/3 is a Type I restriction endonuclease.

FokI cuts about two-fold to four-fold more slowly at CATC^{m5}C than at unmodified sites (P12,N8).

M·FokI in ref P12 corresponds to M·FokIA in ref P13.

HaeII show a reduction in rate of cleavage when its recognition sequence is modified at RGCG^{m5}CY (K16,P2).

HaeIII nicking occurs in the unmethylated strand of the hemi-methylated sequence GG^{m5}CC/GGCC(H1).

HinfI cuts GANT^{m5}C, however, detectable rate differences are observed between unmethylated, hemi-methylated (GANT^{m5}C/GANTC) and bi-methylated (GANT^{m5}C/GANT^{m5}C) target sequences. HinfI does cut phage XP12 DNA, although at a reduced rate (G15,N8). HinfI cuts unmethylated GANTC faster than hemi-methylated GANT^{m5}C/GANTC, which is cut faster than GANT^{m5}C/GANT^{m5}C. However, the rate difference between unmethylated and fully methylated HinfI sites is only about ten-fold (H9,N8,P2).

HpaII nicking occurs in the unmethylated strand of the hemi-methylated sequence ^{m5}CCGG/CCGG. See reference (B37) for HpaII rate effects.

KpnI sensitivity to hemi-methylated GGTA^{m5}CC and GGTAC^{m5}C sites has been reported (P15). However, KpnI efficiently cuts ^{m5}C-substituted phage XP12 DNA and GT^{m6}AC-modified *Chlorella* virus NY2A DNA (N5). It is likely that M·KpnI specifies a ^{m4}C modification.

MaeII nicks slowly in the unmethylated strand of hemi-methylated A^{m5}CGT/ACGT (M25).

MboI isoschizomers that are sensitive to G^{m6}ATC include BssGII, BsaPI, BstXII, BstEIII, CpaI, DpnII, FnuAII, FnuCI, MmeII, MnoIII, MosI, NdeII, NflI, NlaII, NsuI, SinMI (R8).

MboII cuts the fully ^{m5}C-substituted phage XP12 DNA (N8), although certain hemi-methylated ^{m5}C-containing substrates are reported not to be cut (G15).

MflI cuts slowly at ^{m6}AGATCY sites (O1).

M·MmuI is the mammalian ^{m5}CG methyltransferase from *Mus musculus*. (mouse) (B10).

MspI cuts the unmethylated strand and methylated strand of C^{m5}CGG/CCGG (H1,W7) and C^{m4}CGG/CCGG duplexes (B37). MspI cuts very slowly at GGC^{m5}CGG (B33,K6). An M·MspI clone methylates ^{m5}CCGG (W7,W3). However, there is a report that *Moraxella sp.* chromosomal DNA is methylated at ^{m5}C^{m5}CGG (J11).

MvaI nicking occurs in the unmethylated strand of the hemi-methylated sequence C^{m4}CWGG/CCWGG (G13).

NanII requires adenine methylation on both DNA strands (C1). NanII cuts M·Eco dam modified XP12 DNA (N8).

NciI may cut $^{m5}C^{m5}CGG$ methylated DNA (B31,J11). Possibly the second methylation negates the effect of $C^{m5}CGG$.

NcoI is blocked by M·SecI (CCNNGG) (N8).

NcrI is a BglII isoschizomer from *Nocardia carnia* Beijing (Q1).

NdeI cuts the fully ^{m5}C-substituted phage XP12 DNA (N8).

NdeII cuts the fully ^{m5}C-substituted phage XP12 DNA (N8).

NmuDI requires adenine methylation on both DNA strands (C1).

NmuEI requires adenine methylation on both DNA strands (C1).

RsaI cuts the fully ^{m5}C-substituted phage XP12 DNA (N8), but does not cut *Chlorella* virus NY2A DNA, which is modified at $GT^{m6}AC$ (N5,X1). DNA from *Rhodopseudomonas sphaeroides* species Kaplan is cut by Asp718I, but not by RsaI or KpnI (N5). Since both Asp718I and KpnI cut NY2A DNA ($GT^{m6}AC$), it is likely that M·RsaI specifies $GTA^{m4}C$. High levels of ^{m4}C are present in *R. sphaeroides* DNA (E3).

RsrI cannot cut hemi-methylated $G^{m6}AATTC$/GAATTC sites.

Sau3AI nicking occurs in the unmethylated strand of the hemi-methylated sequence $GAT^{m5}C$/GATC (B3,S22). Sau3AI cuts at a reduced rate at $^{m6}AGATC$ (O1). Sau3AI isoschizomers that are insensitive to $G^{m6}ATC$ include Bce243I, Bsp67I, BspAI, BspPII, BsrPII, CpeI, FnuEI, MthI, NsiAI, PfaI (R8).

SfiI cannot cut M·BglI-modified DNA (V1). SfiI cuts M·HaeIII-modified ($GG^{m5}CC$) Ad2 or phage lambda DNA, but does not cut fully ^{m5}C-modified phage XP12 DNA (N5).

SmaI nicking occurs in the unmethylated strand of the hemi-methylated sequence $CC^{m5}CGGG$/CCCGGG (W7,B37). SmaI may cut $C^{m5}C^{m5}CGGG$ methylated DNA (B31,J11) Possibly the second methylation negates the effect of $CC^{m5}CGGG$. There are conflicting results regarding SmaI: $^{m5}CCCGGG$ is not cut when modified by M·AquI methyltransferase (K5) or at overlapping M·HaeIII-SmaI sites ($GG^{m5}CCCGGG$, N8). Other investigators have reported that SmaI cuts at a reduced rate at hemi-methylated $^{m5}CCCGGG$ sites (B37).

SplI cuts $GT^{m5}AC$-modified *Chlorella* virus NY2A DNA, but does not cut KpnI-digested XP12 DNA (N5).

StySBI is a Type I restriction endonuclease. ^{m}T represents a 6-methyladenine in the complementary strand.

StySPI is a Type I restriction endonuclease. ^{m}T represents a 6-methyladenine in the complementary strand.

TaqI cuts very slowly at $T^{hm5}CGA$ (H9). TaqI cuts the fully ^{m5}C substituted phage XP12 DNA (N8).

XbaI will cut $T^{m5}CTAGA$/TCTAGA hemi-methylated DNA at high enzyme levels (>100U Xba I/ug), but will not cut this sequence in twenty to forty-fold overdigestions.

XhoII nicking occurs slowly in the unmethylated strand of the hemi-methylated sequence $RGAT^{m5}CY$/RGATCY.

XmaI is claimed not cut $CC^{m5}CGGG$ in one report (B31). See reference B37 for rate effects.

XmnI cuts the fully ^{m5}C substituted phage XP12 DNA (N8). XmnI cuts slowly at some sites in DNA methylated on *both* strands at $GAAN_4TT^{m5}C$ (N8).

TABLE II: DNA methyltransferases and their modification specificities

Methylase [a]	Specificity [a]	References
M·AccI	GTMK^{m6}AC	L15
M·AflII	CTTAAG (^{m6}A)	L15
M·AlaK21	GAT^{m5}C	S14
M·AluI	AG^{m5}CT	K21
M·ApaI	GGG^{m5}CCC	L5,M18,T1
M·AquI	^{m5}CYCGRG	K5
M·BalI	TGG^{m5}CCA	L15,M18
M·BamHI	GGAT^{m4}CC	B27,H1,L15,N3
M·BamHII	G^{m}CXGC	H1
M·BbvI	G^{m5}CWGC	D5,H1,V7
M·BbvSI	G^{m}CXGC	H1,R7,V7
M·BbvSII	G^{m6}AT	H1
M·BbvSIII	A^{m6}AG	H1
M·BcnI	C^{m4}CSGG	J3,J4,J7,J8,J10,P3,P14
M·BepI	^{m5}CGCG	K9
M.Bme216I	GGWC^{m}C	M9
M·BspRI	GG^{m}CC	F2,K17,P10,S27,V9
M·BstI	GGAT^{m}CC	L10
M·BstYI	RGAT^{m}CY	V4
M·Bsu Phi3T	GG^{m5}CC	G21,G50,N17,N18
	and G^{m5}CNGC	G20,G21,N16,T5
M·BsuP11I	GG^{m5}CC and G^{m5}CNGC	G20,G21,N16,N17,
M·BsuP11s	GGCC	B6
	and GDGCHC	
M·BsuEI	^{m5}CGCG	G20,I1,J12,S27
M·BsuFI	^{m5}CCGG	G20,I1,J12,W9
M·BsuMI	CT^{m5}CGAG	G20,J12,S11
M·BsuQI	^{m}CCGG	J11
M·BsuRI	GG^{m5}CC [b]	K10,K11
M·BsuRII	CT^{m}CGAG	N17
M·BsuSPB	GG^{m5}CC	G20,G21,J11,K10,N16,
	and G^{m5}CNGC	N17,T2,T5
M·BsuSPRI	GG^{m5}CC	G20,G21,N17
	and ^{m5}C^{m5}CGG	P11
	and C^{m5}CXGG	B7,B32,G18,G21,K10,P11
M·BsuSPR191	^{m5}C^{m5}CGG	J11,N17,P11
	and C^{m}CXGG	G18
M·BsuSPR83I	GG^{m5}CC	G18
	and C^{m5}CXGG	G18
M·CfrI	YGG^{m5}CCR	P14
M·Cfr6I	CAG^{m4}CTG	B36
M·Cfr9I	C^{m4}CCGGG	P14
M·Cfr10I	R^{m5}CCGGY	P14
M·Cfr13I	GGN^{m5}CC	B18
M·ClaI	ATCG^{m6}AT	M12

Methylase [a]	Specificity [a]	References
M·CreI	T^{m5}CR	S2 (Chlamydononas)
M·CviJI	RG^{m5}CY	V4
M·CviBI	G^{m6}ANTC	X2,X6
M·CviBIII	TCG^{m6}A	N2
M·Cvi NYI	^{m5}CC	X5
M·CviQI	GT^{m6}AC	X1,X4
M·DdeI	^{m5}CTNAG	H8,S26
M·DpnII	G^{m6}ATC	L1,L2,L3,M7,V11
M·EaeI	YGG^{m5}CCR	J2,W12
M·Eco dam	G^{m6}ATC	B29,B40,D7,G7,H2,H6,U1
M·Eco dcmI	C^{m}CXGG	B24,M10,U1
M·Eco dcmII	R^{m}CCGG	B39,N10
M·Eco dcmIII	^{m}CCXGG	N13
M·Eco dcmIV	GGXC^{m}C	M24,N13
M·EcoA	G^{m6}AGN$_7$G^{m}TCA [b]	C9,F5
M·EcoB	TG^{m6}AN$_8$^{m}TGCT [b]	G10
M·EcoE	G^{m6}AGN$_7$ATGC [b]	C5
M·EcoK	A^{m6}ACN$_6$G^{m}TGC [b]	B21,G10,L13,S1
M·EcoPI	AG^{m6}ACC [b]	H10
M·EcoP1 dam	G^{m6}ATC [b]	C7
M·EcoP15	C^{m6}AGCAG	H10
M·EcoR124	GAAN$_6$RTCG (^{m6}A)	P14
M·EcoR124/3	GAAN$_7$RTCG (^{m6}A)	P14
M·EcoRI	GA^{m6}ATTC	D8,G12,K7,M6, N6,N11,R13
M·EcoRII	C^{m5}CWGG	B11,B38,B39,K13,K18,K19,K20, M10,S19,Y4
M·EcoRV	G^{m6}ATATC	B22
M·EcoT1 dam	G^{m6}ATC	S3
M·EcoT2 dam	G^{m6}ATC	B30,H2,H4,M23,S5
M·EcoT4 dam	G^{m6}ATC	H5,M1,S5
M·Eco57I	CTGAAG (^{m6}A)	P14
M·Eco72I	CACGTG (^{m5}C)	P14
M·FokI	GG^{m6}ATG and C^{m6}ATCC	L15,M8,N20
M·HaeII	RGCGCY	S16
M·HaeIII	GG^{m5}CC [b]	M4,M5,S16
M·HapII	C^{m}CGG	W1
M·HgaI	GACGC (^{m}C)	N20
M·HhaI	G^{m5}CGC	B5,C3,S17,Z2
M·HhaII	G^{m6}ANTC	K6,M2,M3,S8,S17
M·HincII	GTXY^{m6}AC	G15,M18,R12 R4
M·HindII	GTYR^{m6}AC	L15,R7,R11,R12
M·HindIII	^{m6}AAGCTT	L15,R11,R12
M·HinfI	G^{m6}ANTC	C9,L15
M·HpaI	GTTA^{m6}AC	B31,Y3
M·HpaII	C^{m5}CGG	L15,M4,Q2,R6,W16,Y2

Methylase [a]	Specificity [a]	References
M·HphI	T^{m5}CACC	M18,N5,N6
M·MboI	G^{m6}ATC	M18
M·MboII	GAAG^{m6}A	M21,N5,N6
M.Mmu	^{m5}CG [b]	B10 (Mouse)
M·MspI	^{m5}CCGG [b]	E2,J11,N21,R6,V2,V5,W1,W7
M·MvaI	C^{m4}CWGG	B35,P14
M·NcoI	CCATGG (^{m}C)	V1
M·NdeI	CATATG (^{m6}A)	S13
M·NgoII	GG^{m}CC	K15
M·NgoIV	G^{m}CCGGC	C4,K15
M·NgoV	GGNN^{m}CC	K15,P5
M·NgoVI	G^{m6}ATC	K15
M·Ngo VII	G^{m}CXGC	K15
M·NgoAI	GG^{m5}CC	P6
M·NgoBI	T^{m5}CACC	P6
M·NgoBII	GTN^{m5}CTC	P6
M·NlaIII	CATG (^{m}C)	L15
M·PaeR7I	CTCG^{m6}AG	G8,T3,T4
M·PstI	CTGC^{m6}AG	L8,W5,W6,W8
M·PvuII	CAG^{m4}CTG	B19
M·RsrI	GA^{m6}ATTC	B4
M·SalI	GTCG^{m6}AC	L15,R9
M·SmaI	CC^{m}CGGG	L16,P14
M·Sso47I	G^{m6}AATTC	N7
M·Sso47II	C^{m}CNGG	N12,N14
M·SspMQI	^{m5}CG	N19
M·StySBI	G^{m6}AGN$_6$R^{m}TYG [b]	F4,F6,G3,N1
M·StySPI	A^{m6}ACN$_6$G^{m}TRC [b]	F4,F6,N1
M·StySQ	A^{m6}ACN$_6$R^{m}TAYG [b]	F4,F6
M·StySJ	G^{m6}AGN$_6$G^{m}TRC [b]	G3
M·TaqI	TCG^{m6}A	M12,S2a,S15
M·TthHBI	TCG^{m6}A	M12,S2a
M·TflI	TCG^{m6}A	S2a,V8
M·XbaI	TCTAG^{m6}A	V1,M22
M·XmaIII	CGG^{m}CCG	M18,T1

NOTES

a. See footnote "a" of **Table I.**

b. See footnote "b" of **Table I.**

TABLE III: Methylation sensitivity of Type II DNA methyltransferases.

Methylase(specificity)[a]	Not blocked by prior modification at [b]	Blocked by prior modification at [b]	
M·AluI (AG^{m5}CT)		AG^{m4}CT	B36
M·BamHI (GGAT^{m4}CC)	GG^{m6}ATCC	GGATC^{m5}C	L4,M19a
M·BstI (GGAT^{m}CC)[c]	GG^{m6}ATCC		L10
M·Cfr6I (CAG^{m4}CTG)		CAG^{m5}CTG	B36
M·ClaI (ATCG^{m6}AT)	^{m6}ATCGAT		M9,M20,W11
	AT^{m5}CGAT		
M·CviBIII (TCG^{m6}A)	T^{m5}CGA		M19a,V3
M·EcoRI (GA^{m6}ATTC)	GAATT^{m5}C	G^{m6}AATTC	B25
M·EcoRII (C^{m5}CWGG)		C^{m4}CWGG	B35
M·Eco dam (G^{m6}ATC)	GAT^{m5}C [c]		M19a
	GAT^{hm5}C		S6
	GAT^{m4}C		N7
M·FokIA (GG^{m6}ATG)[c]	CATC^{m5}C	CAT^{m5}CC	P12,P13,S4
M·HhaI (G^{m5}CGC)	GCG^{m5}C		R6
M·HhaII (G^{m6}ANTC)	GANT^{m5}C		M19a
M·HpaII (C^{m5}CGG)		^{m5}CCGG	M19,M19a
M·HphI (T^{m5}CACC)	GGTG^{m6}A		M19a
M·MboI (G^{m6}ATC)	GAT^{m5}C		M19a
M·MboII (GAAG^{m6}A)	T^{m5}CTT^{m5}C		M19a
M·MspI (^{m5}CCGG)		C^{m5}CGG	M19a
M·MvaI (C^{m4}CWGG)	C^{m5}CWGG		B35
M·PvuII (CAG^{m4}CTG)		CAG^{m5}CTG	B36
M·EcoT2 dam (G^{m6}ATY)	GAT^{hm5}C		D6,S6
M·EcoT4 dam (G^{m6}ATC)	GAT^{hm5}C		S6
M·TaqI (TCG^{m6}A)	T^{m5}CGA		M19a

a. See footnote "a" of **Table I.**
b. An enzyme is classified as insensitive to methylation if it methylates the modified sequence at a rate that is at least one tenth the rate at which it methylates the unmodified sequence. An enzyme is classified as sensitive to methylation if it is inhibited at least twenty-fold by methylation relative to the unmethylated sequence.
c. See footnote "b" of **Table I.**

TABLE IV: Isoschizomer pairs that differ in their sensitivity to sequence-specific methylation.[a]

Methylated sequence [b]	Isoschizomer pairs [c] Cut by	Not cut by	References
C^{m5}CGG	MspI	HpaII (HapII)	E2,M20
C^{m4}CGG	MspI	HpaII	B37
CC^{m5}CGGG	XmaI (Cfr9I)	SmaI	B37
C^{m5}CWGG	BstNI (MvaI)	EcoRII	B35
G^{m6}ATC	Sau3A (FnuEI)	MboI (NdeII)	G5,L14,M19,R8
GAT^{m5}C	MboI	Sau3A	N5
GAT^{m4}C	MboI	Sau3A	N5
GGTAC^{m5}C	KpnI	Asp718I	M27
GGTA^{m5}C^{m5}C	KpnI	Asp718I	N5
GGWC^{m5}C	AflI	AvaII (Eco47I)	B3,J5,W13
RG^{m6}ATCY	XhoII (BstYI)	MflI	M19,N7
T^{m5}CCGGA	AccIII	BspMII	S4
TC^{m5}CGGA	AccIII	BspMII	S4
TCCGG^{m6}A	BspMII (MroI)	AccIII	K8,N7
TCGCG^{m6}A	Sbo13I (SalDI)	NruI	M20,N7

a. In each row the first column lists a methylated sequence, the second column lists an isoschizomer that cuts this sequence, and the third column lists an isoschizomer that does not cut this sequence.
b. See footnote "a" of **Table I.**
c. An enzyme is classified as insensitive to methylation if it cuts the methylated sequence at a rate that is at least one tenth the rate at which it cuts the unmethylated sequence. An enzyme is classified as sensitive to methylation if it is inhibited at least twenty-fold by methylation relative to the unmethylated sequence.

TABLE V: List of restriction systems referred to in this paper, ordered by recognition sequence length.[a]

CviNY	CC	MosI	GATC	Cfr5I	CCWGG	Bsp1286I	GDGCHC
		MthI	GATC	CfrII I	CCWGG		
CviJI	RGCY	NdeII	GATC	EcaII	CCWGG	AvaI	CYCGRG
		NflI	GATC	EclII	CCWGG	AquI	CYCGRG
MnlI	CCTC	NlaII	GATC	EcoRII	CCWGG		
		NsiAI	GATC	Eco27I	CCWGG	HgiJII	GRGCYC
AluI	AGCT	NsuI	GATC	Eco38I	CCWGG	AosII	GRCGYC
		PfaI	GATC	MphI	CCWGG	AhaII	GRCGYC
BsuFI	CCGG	Sau3A	GATC	MvaI	CCWGG	BanII	GRGCYC
BsuQI	CCGG	SinMI	GATC	TaqXI	CCWGG		
HapII	CCGG					AccI	GTMKAC
HpaII	CCGG	HhaI	GCGC	BcnI	CCSGG		
MspI	CCGG	HinPI	GCGC	NciI	CCSGG	HinCII	GTYRAC
AccII	CGCG	BsuRI	GGCC	BbvI	GCAGC	HgiAI	GWGCWC
BepI	CGCG	HaeIII	GGCC				
BstUI	CGCG	NgoII	GGCC	AvaII	GGWCC	Cfr10	RCCGGY
BsuEII	CGCG			Bme216I	GGWCC		

FnuDII	CGCG
ThaI	CGCG
DpnI	G^{m6}ATC
NanII	G^{m6}ATC
NmuDI	G^{m6}ATC
NmuEI	G^{m6}ATC
Bce243I	GATC
BsaPI	GATC
Bsp67I	GATC
BspAI	GATC
BspPII	GATC
BsrPII	GATC
BssGII	GATC
BstEIII	GATC
BstXII	GATC
CpaI	GATC
CviAI	GATC
DpnII	GATC
FnuAII	GATC
FnuCI	GATC
FnuEI	GATC
MboI	GATC
MmeII	GATC
MnoIII	GATC
NsiI	ATGCAT
Cfr6I	CAGCTG
PvuII	CAGCTG
NdeI	CATATG
NcoI	CCATGG
Cfr9I	CCCGGG
SmaI	CCCGGG
XmaI	CCCGGG
SacII	CCGCGG
PvuI	CGATCG
RshI	CGATCG
XorII	CGATCG
EagI	CGGCCG
XmaIII	CGGCCG
SplI	CGTACG
BsuMI	CTCGAG
BsuRII	CTCGAG
PaeR7I	CTCGAG
XhoI	CTCGAG
CviQI	GTAC
RsaI	GTAC
TaqI	TCGA
TfiI	TCGA
TthI	TCGA
ScrFI	CCNGG
DdeI	CTNAG
CviBI	GANTC
HhaII	GANTC
HinfI	GANTC
Cfr13I	GGNCC
Sau96I	GGNCC
AacI	CCWGG
AorI	CCWGG
ApyI	CCWGG
AtuBI	CCWGG
AtuII	CCWGG
BinSI	CCWGG
BspNI	CCWGG
BstGII	CCWGG
BstNI	CCWGG
Sso47I	GAATTC
SacI	GAGCTC
SstI	GAGCTC
EcoRV	GATATC
SphI	GCATGC
NaeI	GCCGGC
BssHII	GCGCGC
NheI	GCTAGC
BamHI	GGATCC
BamFI	GGATCC
BamKI	GGATCC
BamNI	GGATCC
BstI	GGATCC
BstI	GGATCC
Bst15031	GGATCC
NarI	GGCGCC
Asp718I	GGTACC
KpnI	GGTACC
ApaI	GGGCCC
Eco47I	GGWCC
SinI	GGWCC
EcoPI	AGACC
BspMI	ACCTGC
EcoP15	CAGCAG
FokI	CATCC
MboII	GAAGA
NcuI	GAAGA
EarI	GAAGAG
TaqII	SACCSA
HgaI	GACGC
SfaNI	GATGC
AlwI	GGATC
BinI	GGATC
HphI	TCACC
NgoBI	TCACC
BspHI	TCATGA
RspXI	TCATGA
AccIII	TCCGGA
BspMII	TCCGGA
MroI	TCCGGA
AmaI	TCGCGA
SalDI	TCGCGA
NruI	TCGCGA
Sbo13I	TCGCGA
SpoI	TCGCGA
XbaI	TCTAGA
AtuCI	TGATCA
BclI	TGATCA
BspXII	TGATCA
BstGI	TGATCA
CpeI	TGATCA
FspI	TGCGCA
BalI	TGGCCA
AsuII	TTCGAA
BstBI	TTCGAA
Csp45I	TTCGAA
HaeII	RGCGCY
NgoI	RGCGCY
BstYI	RGATCY
MflI	RGATCY
XhoII	RGATCY
CfrI	YGGCCR
EaeI	YGGCCR
HindIII	AAGCTT
MluI	ACGCGT
SpeI	ACTAGT
BglII	AGATCT
NcrI	AGATCT
Eco47III	AGCGCT
StuI	AGGCCT
BanIII	ATCGAT
BspXI	ATCGAT
ClaI	ATCGAT
XmnI	GAAN$_4$TTC
BglI	GCCN$_5$GGC
EspI	GCTNAGC
BstEII	GGTNACC
CspI	CGGWCCG
RsrII	CGGWCCG
EcoR124	GAAN$_6$RTCG
EcoR124/3	GAAN7RTCG
EcoK	AACN$_6$GTGC
StySPI	AACN$_6$GTRC
EcoE	GAGN$_7$ATGC
EcoA	GAGN$_7$GTCA
StySBI	GAGN$_6$RTAYG
EcoDXXI	TCAN$_7$ATTC
EcoB	TGAN$_8$TGCT
NotI	GCGGCCGC

PstI	CTGCAG	SalI	GTCGAC	BstXI	$CCAN_6TGG$	SfiI	$GGCCN_5GGCC$
SfiI	CTGCAG	ApaLI	GTGCAC				
EcoRI	GAATTC			MstII	CCTNAGG		
RsrI	GAATTC	HpaI	GTTAAC				

Note:
a. Restriction systems in **Table V** are arranged by recognition sequence length and alphabetically by recognition sequence to aid in identifying isoschizomers.

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*To whom correspondence should be addressed

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