Site-specific methylation: effect on DNA modification methyltransferases and restriction endonucleases

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INTRODUCTION

We present in **Table I** an updated list of the sensitivities of over 240 restriction endonucleases to the site-specific DNA modifications ^{m4}C, ^{m5}C, ^{hm5}C, and ^{m6}A, four modifications that are common in DNA prokaryotes, eukaryotes, and their viruses (Mc2,Mc5,Mc8,Mc11,Ne3,Ne4).

Table II is a list of over 130 characterized DNA methyltransferases. A detailed list of cloned restriction-modification genes has been made Wilson (Wi4).

Table III lists the sensitivities of over 20 Type II DNA methyltransferases to ^{m4}C, ^{m5}C, ^{hm5}C, and ^{m6}A modification. Most DNA methyltransferases are sensitive to non-canonical modifications within their recognition sequences (Bu5,Mc10,Ne3,Po4), and this sensitivity may differ from that of their restriction endonuclease partners.

Finally, several restriction endonuclease isoschizomers are known to differ in their ability to cleave DNA which has been methylated. **Table IV** lists over 20 known isoschizomer pairs and one isomethylator pair, along with the modified recognition sites at which they differ.

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 frequently methylated at these positions. Endonucleases that are unaffected by these two cytosine modifications include: *Acc*III, *Afl*II, *Aha*III, *Ase*I, *Asp*700I *Asu*II, *Bbu*I, *Bcl*I, *Bsp*HI, *Bsp*NI, *Bst*EII, *Bst*NI, CviQI, *Dpn*I, *Dra*I, *Eco*RV, *Hin*CII, *Hpa*I, *Kpn*I, *Mbo*II, *Mse*I, *Nde*I, *Nde*II, *Pac*I, *Rsa*I, *Rsp*XI, *Spe*I, *Sph*I, *Ssp*I, *Swa*I, *Taq*I, *Tth*HBI and *Xmn*I.

CpG sequences occur infrequently and are often methylated in mammalian genomes (Mc9). Almost all the enzymes that could generate large fragments of mammalian DNA are blocked by this ^{m5}CpG modification at overlapping sites, including *Aat*II, *Ape*I, *Avi*II, *Bbe*I, *Bma*DI, *Bss*HII, *Bsp*MII, *Bst*BI, *Cla*I, *Csp*I, *Csp*45I, *Eag*I, *Ecl*XI, *Eco*47III, *Fse*I, *Fsp*I, *Kpn*2I *Mlu*I, *Mlu*9273I, *Mlu*9273II, *Mro*I, *Nae*I, *Nar*I, *Not*I, *Nru*I, *Pfu*I, *Pml*I, *Ppu*AI, *Pvu*I, *Rsr*II, *Sal*I, *Sal*DI, *Sbo*13I, *Sfi*I, *Sma*I, *Sna*BI, *Spl*I, *Spo*I, *Xho*I and *Xor*II (see **Table I**).

Only four enzymes suitable for pulsed field mapping of eukaryotic chromosomes are known to cut ^{m5}CG-modified DNA: *Acc*III, *Asu*II, *Cfr*9I and *Xma*I. It has been determined that *Sfi*I is sensitive to ^{m5}C modification at the second cytosine of its recognition sequence, GGC^{m5}CN$_5$GGCC. *Sfi*I is therefore sensitive to overlapping ^{m5}CG methylation at GGC^{m5}CGN$_4$GGCC sites in mammals and overlapping *dcm* methylation at GGC^{m5}CWGGNNGGCC sequences in *E. coli*..

^{m4}C and ^{m5}C Cytosine modifications

In some cases, a restriction enzyme may differ with to sensitivity to ^{m4}C and ^{m5}C at a particular sequence. For example, *Bst*NI and *Mva*I cut ^{m5}C, but not ^{m4}C modified CCWGG sequences. *Kpn*I cuts GGTAC^{m5}C but not GGTAC^{m4}C. *Bst*YI cuts RGAT^{m5}CY but not RGAT^{m4}CY. Restriction enzymes we have tested for sensitivity to ^{m4}C include: *Aat*I, *Afl*I, *Alw*I, *Ava*II, *Ban*I, *Bgl*I, *Bst*I, *Bst*NI, *Bst*YI, *Dpn*I, *Fok*I, *Mbo*I, *Mva*I, *Nar*I, *Nci*I, *Pfl*MI, *Sau*3A, and *Scr*FI.

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 site-specific DNA methylation can interfere with many sequence-specific DNA binding proteins (e.g. St2,Wa8) including binding of restriction endonucleases and DNA methyltransferases. DNA methylation may cause long-range perturbations of DNA minor and major grooves, and a range of rate effects are observed when modified substrates are used in restriction-modification reactions. Results can be summarized as follows.

(1) Canonical site-specific methylation *always* inhibits DNA cleavage by a restriction endonuclease. For example, M.*Bam*HI methylase modifies GGAT^{m4}CC; and *Bam*HI endonuclease cannot cut this methylated sequence.

(2) In about one half of the cases tested, methylation at non-canonical sites inhibits the rate of duplex DNA cleavage at least ten-fold (**Table I**). However, in other cases non-canonical methylation has no effect on restriction cleavage. For example, *Bam*HI cuts DNA which has been modified at GGATC^{m4}C or GGATC^{m5}C, but cannot cut DNA methylated at GGAT^{m5}CC.

(3) There are a few examples in which non-canonical methylation slows the rate of cleavage or permits nicking of one strand of a hemi-methylated duplex. Examples of such rate effects are presented in footnotes to **Table I**.

(4) Sometimes base modifications which lie *outside* a recognition sequence can influence the rate of DNA cleavage by a restriction enzyme. For example, *Nar*I does not cut at overlapping M.*Mva*I-*Nar*I *GGCGCC*^{m4}CCWGG sites (Ne1); and *Hae*III cannot cut certain GGCC^{m}T sites, where ^{m}T are modifed thymine residues (Wi1). Such methylation-induced 'action at a distance' may be more common than has been

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previously appreciated. We have tested only a few enzymes for sensitivity to base modifications *outside* their canonical recognition sequences.

Effect of site-specific methylation on DNA methyltransferases

Twenty-three Type II methyltransferases have been tested for sensitivity to *non-canonical* DNA modifications, of which nine were blocked (Mc10 and **Table III**). As with restriction endonucleases, rate effects are sometimes seen with DNA methyltransferases at non-canonically modified sequences. For example, *E. coli Dam* methyltransferase is unaffected by G-AT^{m4}C, but methylates GAT^{m5}C relatively slowly. Such data is summarized in **Table III** and footnotes to **Table I**.

Methylase/endonuclease combinations can produce novel DNA cleavage specificities

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

For example, certain adenine methyltransferases may be used in conjunction with the methylation-dependent restriction endonuclease *Dpn*I to create cleavages at eight- to twelve-base-pair sequences (Mc6,Mc12). M·*Cla*I and *Dpn*I have been used to cut the 2.8 million base pair *Staphylococcus aureus* genome into two pieces at the sequence ATCGATCGAT (We1). Twelve-base-pair TCTAGATCTAGA M·*Xba*I/*Dpn*I sites in a transposon have been introduced into bacterial genomes and permit cleavage one or more times depending on the number of transposons integrated (Ha5).

Protection of a subset of restriction endonuclease cleavage sites by methylation at overlapping methyltransferase/endonuclease targets has been described (Hu1,Kl1,Ne6). This two-step 'cross-protection' strategy has produced over 60 new cleavage specificities, and many more are possible (Ja2,Ka2,Kl1,Ne6). Extremely specific DNA cleavages may result from certain 'cross-protections.' For example, M·*Fnu*DII/*Not*I cleavage has been used to cut the 4.7 million base pair E. coli K12 genome into fourteen pieces (Qi2).

Methylases have been used to compete with endonucleases for recognition sites in a method called methylase-limited partial digestion. This method is particularly useful for performing partial digests in agarose plugs for pulsed field gel electrophoresis (Ha6). Blocking a subset of DNA methyltransferase sites by overlapping methylation (sequential double-methylation) can expose a subset of restriction endonuclease sites for cleavage (Mc9,Ne3,Po3). For instance, M·*Hpa*II, M·*Bam*HI, and *Bam*HI have been used in a sequential three-step methyltransferase/methyltransferase/endonuclease reaction to achieve selective DNA cleavage at the ten base pair sequence, CCGG-ATCCGG (Mc10).

Polypyrimidine oligonucleotides have been used in DNA triplexes to selectively mask restriction-modification sites. For example, polyppyrimidine triplexes which overlap M.*Taq*I sites have been used to enable selective restriction cleavage (Ma7).

Finally, methods based on the sequential use of purified lac repressor protein, DNA methyltransferases, and restriction endonucleases have been used to achieve highly selective DNA cleavages (Ko2).

Methylation-dependent restriction systems in bacteria

E. coli K-12 contains at least three different methylation-dependent restriction systems which selectively restrict methylated target sequences: *mrr* (^{m6}A), *mcr*A (^{m5}CG), *mcr* B (R^{m5}C) (Br5,Di1,He3,Ra1,Ra2). *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 *mcr*A (Wo2). Appropriate non-restricting strains of *E. coli* (Go2,Kr1, Ra1,Ra2) should be chosen for efficient transformation and cloning of methylated DNA. Other species have such restriction systems (e.g. Ma2).

Engineered altered methylase specificities

Many methylase gene have now been sequenced. Extensive homologies between closely related enzymes (Wi3) or common motifs (Po5,Sm3) allow new specificities to be developed (e.g. Ba4,Tr4).

Data in electronic form

This paper is available as a text file on a 3.5' Macintosh diskette. The data can be supplied as a Microsoft Word, Macwrite or MS-DOS file. Please contact Michael McClelland at CIBR, phone 619 535 5486, FAX 619 535 5472. There are tentative plans to provide the supplement issue on a CD-ROM.

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TABLE I: Methylation sensitivity of restriction endonucleases [a]

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
AacI	CCWGG	C^{m5}CWGG	?	Br8
AatI	AGGCCT	?	AGG^{m5}CCT	Ne1
			AGGC^{m5}CT	So3
			AGGC^{m4}CT	Ne1
AatII	GACGTC	?	GACGT^{m5}C	Ne1
			GA^{m5}CGTC	Fo1
AccI	GTMKAC	?	GTMK^{m6}AC#	Lu2,Mc3
			GTMKA^{m5}C	
AccII	CGCG	?	^{m5}CGCG	Ga2
AccIII	TCCGGA	T^{m5}CCGGA	TCCGG^{m6}A	Ke3,La2,Sc2
		TC^{m5}CGGA		
AflI	GGWCC	GGWC^{m5}C ??	?	Mc11,Wh2
		GGWC^{m4}C		
AflII	CTTAAG	?	^{m5}CTTAAG	Ne1
			CTTA^{m6}AG	
AflIII	ACRYGT	?	A^{m5}CRYGT	Ne1
AhaII	GRCGYC [b]	?	GR^{m5}CGYC	Ka2,Hu1
			GRCGY^{m5}C	
AluI	AGCT	?	^{m6}AGCT	Gr4,Mc11,Ne2
			AG^{m4}CT	
			AG^{m5}CT#	Hu1,Wo1
			AG^{hm5}CT	Bu5
AlwI	GGATC	?	GG^{m6}ATC	Ne4
			GGAT^{m4}C	
AmaI	TCGCGA	TCGCG^{m6}A	?	Mc13
AosII	GRCGYC	?	GR^{m5}CGYC	Eh2,Gr4,Va3
ApaI	GGGCCC	?	GGG^{m5}CCC#	La9,Tr2
			GGGCC^{m5}C	
ApeI	ACGCGT	?	A^{m5}CGCGT	Ne1,Qi2
ApaLI	GTGCAC	GTGC^{m6}AC	GTGCA^{m5}C	Fo1,Ho1,Ho2
ApyI	CCWGG	C^{m5}CWGG [b]	^{m5}CCWGG	Kl1,Mc11,Ra3
AquI	CYCGRG	?	^{m5}CYCGRG#	Ka7,Ka8
AseI	ATTAAT	ATT^{m6}AAT	?	Ne1
Asp700I	GAAN$_4$TTC	GA^{m6}AN$_4$TTC	G^{m6}AAN$_4$TTC	Ne1
		GAAN$_4$TT^{m5}C		
Asp718I	GGTACC	GGT^{m6}A^{m5}CC [b]	GGTAC^{m5}C	Mu1,Ne4
			GGTA^{m5}C^{m5}C [b]	
AsuII	TTCGAA	TT^{m5}CGAA	?	Ne1
AtuCI	TGATCA	?	TG^{m6}ATCA	Ro3,Sc12
AvaI	CYCGRG	C^{m5}CCGGG	^{m5}CYCGRG	Eh2,Ne1
			CY^{m5}CGRG	Ka4,Ka7,Mc11
			CTCG^{m6}AG [b]	Ne2

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
AvaII	GGWCC	GGWC^{m4}C [b]	GGW^{m5}CC	Ba3,Ko3
			GGWC^{m5}C	Mc10,Mc11
			GGW^{hm5}C^{hm5}C	Hu1
AviII	AGCGCT	^{m6}AGCGCT	AG^{m5}CGCT	Ne1
BalI	TGGCCA	?	TGG^{m5}CCA#	Gi1,Tr2
			TGGC^{m5}CA [b]	
BamHI	GGATCC	GGATC^{m5}C	GGAT^{m4}CC#	Br8,Dr1,Ha1,Hu1
		GG^{m6}ATCC	GGAT^{m5}CC	La7
		GG^{m6}ATC^{m5}C	GGAT^{hm5}C^{hm5}C	
		GGATC^{m4}C		
BamFI	GGATCC	GG^{m6}ATCC	GGAT^{m4}CC	An1,Sh1
BamKI	GGATCC	GG^{m6}ATCC	GGAT^{m4}CC	An1,Sh1
BanI	GGYRCC [b]	GG^{m5}CGCC	?	Co3,Ka2
		GGYRC^{m4}C		
BanII	GRGCYC	GRGCY^{m5}C	GRG^{m5}CYC	Fo1,Ne2,Ne6
BanIII	ATCGAT	?	ATCG^{m6}AT	Su1
BbeI	GGCGCC	GGCG^{m5}CC	GG^{m5}CGCC	Co3,Ne2,Sh2
		GGCGC^{m5}C		
BbiII	GRCGYC	?	GR^{m5}CGYC	Co3
BbrPI	CACGTG	?	^{m5}CA^{m5}CGTG	Wo1
BbsI	GAAGAC	GAAGA^{m5}C	?	Fo1
BbvI	GCWGC	?	G^{m5}CWGC#	Do1,Ha1,Va5
BclI	TGATCA [b]	TGAT^{m5}CA	TG^{m6}ATCA	Bi4,Br8,Eh3,Ro3
			TGAT^{hm5}CA	Hu1
BcnI	CCSGG	^{m5}CCSGG	C^{m4}CSGG#	Ja3,Ja6,Kl1
BepI	CGCG	?	^{m5}CGCG	Ku2
BfrI	CTTAAG	?	^{m5}CTTAAG	Wo1
BglI	GCCN$_5$GGC	GC^{m5}CN$_5$GGC [b]	G^{m5}CCN$_5$GGC	Kl1,Ko3,Mc11,Ne2
			GCCN$_5$GG^{m5}C [b]	
			GC^{m4}CN$_5$GGC [b]	
BglII	AGATCT [b]	AG^{m6}ATCT	AGAT^{m5}CT	Bi4,Br8,Dr1,Dy1,Eh3
			AGAT^{hm5}CT	Hu1,Pi6
BinI	GGATC	?	GG^{m6}ATC	Bo1
BmaDI	CGATCG	CG^{m6}ATCG	CGAT^{m6}CG	Qi2
Bme216I	GGWCC	?	GGWC^{m5}C	Ma9
BnaI	GGATCC	GG^{m6}ATCC	GGAT^{m4}CC	Ne1
			GGAT^{m5}CC#	
BsaI	GGTCTC	?	GGTCT^{m5}C	Fo1
BsaAI	YACGTR	?	YA^{m5}CGTR	Fo1
BsaBI	GATN$_4$ATC	?	GATN$_4$AT^{m5}C	Fo1
BsmI	GAATGC	GAATG^{m5}C	G^{m6}AATGC	Fo1,Ne1
BsmAI	GTCTC	?	GTCT^{m5}C	Fo1
Bsp106I	ATCGAT	?	ATCG^{m5}AT#	Ne5

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
Bsp1286I	GDGCHC	GDGCH^{m5}C	GDG^{m5}CHC	Fo1,Ne2,Ne6
BspHI	TCATGA	?	TC^{m6}ATGA	Pa2
			TCATG^{m6}A	Mc1
BspMI	ACCTGC	ACCTG^{m5}C	?	Fo1
BspMII	TCCGGA	TCCGG^{m6}A	T^{m5}CCGGA	La2,Sc2
			TC^{m5}CGGA	
BspNI	CCWGG	^{m5}CCWGG	?	Ne4
		C^{m5}CWGG		
BspXI	ATCGAT	?	ATCG^{m6}AT	Zi1
BspXII	TGATCA	?	TG^{m6}ATCA	Zi1
BssHII	GCGCGC [b]	?	G^{m5}CGCGC	Ne4,Qi3
BstI	GGATCC	GG^{m6}ATCC	GGAT^{m4}CC	Ne4
		GGATC^{m5}C	GGAT^{m5}CC	
			GGATC^{m4}C	Ne1
BstBI	TTCGAA	?	TTCG^{m6}AA	Ne4
			TT^{m5}CGAA	Wo1
BstEII	GGTNACC	GGTNA^{m5}C^{m5}C [b]	GGTNA^{hm5}C^{hm5}C	Hu1,Mc11
		GGTNAC^{m4}C		Ne1
BstEIII	GATC [b]	?	G^{m6}ATC	My1,Ro3
BstGI	TGATCA	?	TG^{m6}ATCA	Ro3
BstNI	CCWGG [b]	^{m5}CCWGG [b]	^{hm5}C^{hm5}CWGG	Gr4,Hu1,Mc11,Ro3
		C^{m5}CWGG	C^{m4}CWGG	Ne1
		^{m5}C^{m5}CWGG [b]		
BstUI	CGCG	?	^{m5}CGCG	Ne5
BstXI	CCAN$_6$TGG	?	^{m5}CCAN$_6$TGG	Ne2
BstYI	RGATCY	RG^{m6}ATCY	RGAT^{m4}CY	Ne4
		RGAT^{m5}CY		Ne1
BsuBI	CTGCAG	?	CTGC^{m6}AG#	Ga1,Je1,St5,Sh1
BsuEI	CGCG	?	^{m5}CGCG#	Ga1,Je1,St5,Sh1
BsuFI	CCGG	?	^{m5}CCGG#	Je1
BsuMI	CTCGAG	?	CT^{m5}CGAG#	Je1
BsuQI	CCGG	?	^{m}CCGG	Je2
BsuRI	GGCC	?	GG^{m5}CC# [b]	Gu6,Ki2,Ki3
CcrI	CTCGAG	?	CTCG^{m6}AG	Ne1
CfoI	GCGC	?	G^{m5}CGC	Eh1
			G^{hm5}CG^{hm5}C	Hu1
CfrI	YGGCCR	?	YGG^{m5}CCR#	Kl1
Cfr6I	CAGCTG	?	CAG^{m4}CTG#	Bu5
			CAG^{m5}CTG	
Cfr9I	CCCGGG [b]	C^{m5}CCGGG	^{m4}CCCGGG	Bu6
		CC^{m5}CGGG	^{m5}CCCGGG	
			C^{m4}CCGGG#	
			CC^{m4}CGGG	

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
Cfr10I	RCCGGY	?	R^{m5}CCGGY#	Bi5,Kl1
Cfr13I	GGNCC	?	GGN^{m5}CC#	Bi5,Kl1
ClaI	ATCGAT	?	^{m6}ATCGAT	Ca4,Mc11,Mc12,Ne4
			AT^{m5}CGAT	Wo1
			ATCG^{m6}AT#	Mc3
CpeI	TGATCA	?	TG^{m6}ATCA	Fi1,Ro3
CspI	CGGWCCG	CGGWC^{m5}CG	CGGW^{m5}CCG	Mc11
			^{m5}CGGWCCG	
Csp45I	TTCGAA	?	TTCG^{m6}AA	Ne4,Sc11
CtyI	GATC	?	G^{m6}ATC#	Ri2
CviAI	GATC	?	G^{m6}ATC	Xi1,Xi6
CviBI	GANTC	?	G^{m6}ANTC#	Xi3
CviJI	RGCY	?	RG^{m5}CY#	Sh3,Xi2
CviPI	CC	C^{m5}C	^{m5}CC#	Xi4
CviQI	GTAC	GTA^{m5}C	GT^{m6}AC#	Xi2,Xi5
DdeI	CTNAG	?	^{m5}CTNAG#	Ho3,Ne2
			^{hm5}CTNAG	Hu1
DpnI	G^{m6}ATC [b]	G^{m6}ATC	GATC	La3,Mc11,Vo1
		G^{m6}AT^{m5}C [b]	GAT^{m4}C	Ne4
		G^{m6}AT^{m4}C	GAT^{m5}C	Ne5
DpnII	GATC	?	G^{m6}ATC#	De1,La3,La4,La5,Ma6,Vo1
DraI	TTTAAA	TTTA^{6}AA	?	Ne1
DraII	RGGNCCY	?	RGGNC^{m5}CY	Sc8
EaeI	YGGCCR	?	YGG^{m5}CCR#	Ja2,Wh1
			YGGC^{m5}CR	
EagI	CGGCCG	?	CGG^{m5}CCG	Mc11
			^{m5}CGGC^{m5}CG	
EarI	GAAGAG	?	G^{m6}AAGAG	Ne4
			GAAG^{m6}AG	
			^{m5}CT^{m5}CTT^{m5}C	Ne1
EcaI	GGTAN^{m6}ACC	?	GGTA^{m6}ACC#	Br2
EclXI	CGGCCG	?	^{m5}CGGC^{m5}CG	Qi3
			CGG^{m5}CCG	
Eco47I	GGWCC	?	GGWC^{m5}C	Ja5
Eco47III	AGCGCT	^{m6}AGCGCT	AG^{m5}CGCT	Ne1,Ne4
EcoA	GAGN$_7$GTCA [b]	?	G^{m6}AGN$_7$G^{m}TCA# [b]	Bi2,Co6,Fu2
EcoB	TGAN$_8$TGCT [b]	?	TG^{m6}AN$_8$^{m}TGCT # [b]	Bi2,La10,La11
EcoDXXI	TCAN$_7$AATC [b]	?	TCAN$_7$^{m6}AA^{m}TC # [b]	Pi1
EcoE	GAGN$_7$ATGC	?	G^{m6}AGN$_7$ATGC	Co6,Fu2
EcoK	AACN$_6$GTGC [b]	?	A^{m6}ACN$_6$G^{m}TGC# [b]	Bi2,Bi3,Ka1
EcoO109I	RGGNCCY	?	RGGNC^{m5}CY	Sc8
EcoPI	AGACC [b]	AGA^{hm5}C^{hm5}C	AG^{m6}ACC#	Ba1,Ba2,Ha2,Re4
EcoP15	CAGCAG [b]	?	C^{m6}AGCAG#	Hu2

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
EcoRI	GAATTC	GAATT^{hm5}C	G^{m6}AATTC [b]	Mc11,Ne2,Ru1
			GA^{m6}ATTC#	Br1,Br8,Du1
			GAATT^{m5}C [b]	Hu1,Ka3,Ta1
EcoRII	CCWGG	^{m5}CCWGG [b]	^{m4}CCWGG	Ku3,Yo1
			C^{m4}CWGG	Bu4,Na5,Ro3
			C^{m5}CWGG#	Bo5,Mc11
			CC^{m6}AGG	Bu3
			^{hm5}C^{hm5}CWGG	Hu1,Ka3
EcoRV	GATATC	GATAT^{m5}C [b]	G^{m6}ATATC#	Mc11,Ne2,Wo1
			GAT^{m6}ATC	Fl1
EcoR124	GAAN$_6$RTCG [b]	?	GA^{m6}AN$_6$RTCG	Pr2,Pr3
			GAAN$_6$R^{m}TCG	Bi1
EcoR124/3	GAAN$_7$RTCG [b]	?	m6A	Pr1,Pr2
EheI	GGCGCC	?	GGCGCC	Co2
EspI	GCTNAGC	GCTNAG^{m5}C	G^{m5}CTNAGC	Ne4
Fnu4HI	GCNGC	?	G^{m5}CNGC	Ko3,Tr2
			GCNG^{m5}C	
FnuDII	CGCG	?	^{m5}CGCG	Ga1,Ga2,Ne2,Ne6,St6
			CG^{m5}CG	
FnuEI	GATC	G^{m6}ATC [b]	?	Lu1,Ne2
FokI	CATCC	CAT^{m5}CC	GG^{m6}ATG	Po3,Po4,Sc2
		CATC^{m5}C [b]	C^{m6}ATCC	
		CATC^{m4}C		Ne1
FseI	GGCCGGCC	?	GG^{m5}CCGG^{m5}CC	Ne7
			GGC^{m5}CGGCC	
			GG^{m5}CCGGCC	
FspI	TGCGCA	?	TG^{m5}CGCA	Ne4
HaeII	RGCGCY [b]	?	RG^{m5}CGCY	Eh2,Gr4,Ka2,Ko3,Mc11,Pi5
			RG^{hm5}CG^{hm5}CY	Hu1
HaeIII	GGCC	GGC^{m5}C	GG^{m5}CC# [b]	Ba3,Ka2,Ko3,Ma5
			GG^{hm5}C^{hm5}C	Hu1
HapII	CCGG	?	C^{m5}CGG#	Eh2,Wa1
HgaI	GACGC	?	GA^{m5}CGC	Ne1
			GACG^{m5}C	Mc11
HgiAI	GRGCYC	GRGCY^{m5}C	GRG^{m5}CYC	Fo1,Ne2,Wh3
HgiCI	GGYRCC	?	GGYRC^{m5}C	Er1
HgiCII	GGWCC	?	GGWC^{m5}C	Er1
HgiEI	GGWCC	?	GGWC^{m5}C	Er1
HgiJII	GGYRCC	?	GGYRC^{m5}C	Wh3
HhaI	GCGC	?	G^{m5}CGC#	Eh2,Ko3,Sm1
			GCG^{m5}C	Mc11,
			G^{hm5}CG^{hm5}C	Hu1

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
HhaII	GANTC	?	G^{m6}ANTC#	Ma5
HincII	GTYRAC	GTYRA^{m5}C	GTYR^{m6}AC	Gr4,Ro7
			GTYRA^{hm5}C	Hu1
HindII	GTYRAC	?	GTYR^{m6}AC#	Ro7
HinfI	GANTC	GANT^{m5}C [b]	G^{m6}ANTC	Ch1,Co1,Ne2,Pe1
			GANT^{hm5}C	Hu1
HindIII	AAGCTT	?	^{m6}AAGCTT#	Br8,Gr4,Ro7
			AAG^{m5}CTT	Ne2
			AAG^{hm5}CTT	Hu1,Ka3
HinPI	GCGC	?	G^{m5}CGC	Mc11,Ne6
HpaI	GTTAAC	GTTAA^{m5}C	GTTA^{m6}AC#	Br8,Gr4,Hu1,Yo3
			GTTAA^{hm5}C	Hu1
HpaII	CCGG	?	^{m4}CCGG	Be3,Bu6,Eh2,Ma5
			^{m5}CCGG [b]	Ko3,Qu1,Wa5
			C^{m4}CGG [b]	
			C^{m5}CGG#	
			^{hm5}C^{hm5}CGG	Hu1
HphI	TCACC	TCAC^{m5}C	T^{m5}CACC#	Fo1,Mc11,Ne2
			GGTG^{m6}A	
KpnI	GGTACC [b]	GGTA^{m5}CC	GGT^{m6}A^{m5}CC	Eh3,Mc11,Ne2
		GGTAC^{m5}C	GGTAC^{m4}C	Ne1
		GGTA^{m5}C^{m5}C [b]		
Kpn2I	TCCGGA	TCCGG^{m6}A	T^{m5}CCGGA	Mc1,Ne1
			TC^{m5}CGGA	Ne1
KspI	CCGCGG	?	^{m5}CCGCGG	Ne1
			C^{m5}CGCGG	Qi2
MaeII	ACGT	?	A^{m5}CGT [b]	Mo2
MamI	GATN$_4$ATC	?	G^{m6}ATN$_4$^{m6}ATC	St4
MboI	GATC [b]	GAT^{m4}C	G^{m6}ATC#	Br5,Ge1,Mc8
		GAT^{m5}C [b]	GAT^{hm5}C	Hu1,Ro3
MboII	GAAGA	T^{m5}CTT^{m5}C [b]	GAAG^{m6}A#	Ba3,Mc11,Mc12,Ne2
		G^{m6}AAGA		
MflI	RGATCY [b]	?	RG^{m6}ATCY	On1
			RGAT^{m4}CY	
			RGAT^{m5}CY	
MluI	ACGCGT	^{m6}ACGCGT	A^{m5}CGCGT	Mc11,Sh1,St5,Qi3
Mlu9273I	TCGCGA	?	T^{m5}CGCGA	Ne1
Mlu9273II	GCCGGC		G^{m5}CCGGC	Ne1
			GC^{m5}CGGC	
MmeII	GATC	?	G^{m6}ATC	Bo4
MnlI	CCTC [b]	?	^{m5}CCTC	Eh3,Mc11
			^{m5}C^{m5}CT^{m5}C	

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
MphI	CCWGG [b]	?	$C^{m5}CWGG$	Ro3
MroI	TCCGGA	$TCCGG^{m6}A$	$T^{m5}CCGGA$	Mc1,Ne1
			$TC^{m5}CGGA$	Ne1
MseI	TTAA	$TT^{m6}AA$	?	Ne1
MspI	CCGG [b]	$^{m4}CCGG$	$^{m5}CCGG$#	Eh2,Je2,Va3,Wa1,Wa5
		$C^{m4}CGG$	$^{hm5}C^{hm5}CGG$	Bu6,Hu1
		$C^{m5}CGG$		
MstII	CCTNAGG	$^{m5}CCTNAGG$	?	Mc11
MvaI	CCWGG	$C^{m5}CWGG$ [b]	$C^{m4}CWGG$#	Bu4,Ku1
		$^{m5}CCWGG$	$CC^{m6}AGG$ [b]	Gr3,Ku3
			$^{m4}CCWGG$ [b]	
			$^{m5}C^{m5}CWGG$ [b]	Ne1
MvnI	CGCG	?	$^{m5}CGCG$	Ne1
NaeI	GCCGGC [b]	?	$G^{m5}CCGGC$	Eh3,Kl1,Mc11,Ne5
			$GC^{m5}CGGC$	
			$GCCGG^{m5}C$	
NanII	$G^{m6}ATC$ [b]	$G^{m6}ATC$	GATC	Pa1,Ne5
		$G^{m6}AT^{m5}C$ [b]	$GAT^{m5}C$	
NarI	GGCGCC	$GGCGC^{m5}C$	$GG^{m5}CGCC$	Ko3,Mc11,Ne5
			$GGCGC^{m4}C$	Ne1
NciI	CCSGG	$^{m5}CCSGG$	$C^{m4}CSGG$	Br8,Ko3,Mc11
			$C^{m5}CSGG$ [b]	
NcoI	CCATGG	$CC^{m6}ATGG$	$^{m4}CCATGG$ [b]	Kl1,Ne2,Ne4
			$^{m5}CCATGG$	
NcrI	AGATCT	$AG^{m6}ATCT$ [b]	?	Qi1
NcuI	GAAGA	$GAAG^{m6}A$	?	Mc13
NdeI	CATATG	$^{m5}CATATG$ [b]	^{m6}A	Be4,Mc11
NdeII	GATC	$GAT^{m5}C$ [b]	$G^{m6}ATC$	Mc9
NgoBI	TCACC	?	$T^{m5}CACC$	Pi3,Pi4
NgoPI	RGCGCY	?	$RG^{m5}CGCY$	Ko3,Ko5
NgoPII	GGCC	?	$GG^{m5}CC$#	Ko3,Ko5
			$GGC^{m5}C$[b]	Su3,Su4
NheI	GCTAGC	?	$GCTAG^{m5}C$	Kl1,Mc11,Ne2
NlaIII	CATG	?	$C^{m6}ATG$#	La1,Mo3
NmuDI	$G^{m6}ATC$ [b]	$G^{m6}ATC$	GATC	Pa1
NmuEI	$G^{m6}ATC$ [b]	$G^{m6}ATC$	GATC	Pa1
NotI	GCGGCCGC	$GCGGCCG^{m5}C$	$GCGG^{m5}CCGC$	Mc11
			$GCGGC^{m5}CGC$	St5,Qi2
NruI	TCGCGA	$TCG^{m5}CGA$	$T^{m5}CGCGA$	Ne1,Qi3
			$TCGCG^{m6}A$	Ne2
NsiI	ATGCAT	?	$ATGC^{m6}AT$	Be5
			$ATG^{m5}CAT$	Wo1

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
NspBII	CMGCKG	$C^{m5}CGCKG$	?	Ne1
PflMI	$CCAN_5TGG$	?	$C^{m4}CAN_5TGG$	Ne1
			$C^{m5}CAN_5TGG$	St7
PfaI	GATC	$G^{m6}ATC$	?	Ro3
PfuI	CGTACG	?	$CGTA^{m5}CG$	Ne1
PaeR7I	CTCGAG	?	$CTCG^{m6}AG$#	Gi3
			$CT^{m5}CGAG$	Gh1
PmlI	CACGTG	?	$CA^{m5}CGTG$	Fo1
PpuAI	CGTACG	?	$CGTA^{m5}CG$	Ne1
PstI	CTGCAG	?	$^{m5}CTGCAG$	Do1,Gr4,Mc11,Ne2
			$CTGC^{m6}AG$#	
PvuI	CGATCG [b]	$CG^{m6}ATCG$	$CGAT^{m4}CG$	Br8,Bu3,Eh3
			$CGAT^{m5}CG$	
PvuII	CAGCTG	?	$CAG^{m4}CTG$#	Br8,Bu5,Do1
			$CAG^{m5}CTG$	Eh3,Ja3,Ro1
Rrh4273I	GTCGAC	?	$GTCG^{m6}AC$	Ba6
RsaI	GTAC [b]	$GTA^{m5}C$ [b]	$GT^{m6}A^{m5}C$	Eh3,Ne4,Ne5
RshI	CGATCG	$CG^{m6}ATCG$	?	Ly1
RspXI	TCATGA	?	$TC^{m6}ATGA$	Pa2
			$TCATG^{m6}A$	Ne4
RsrI	GAATTC	?	$G^{m6}AATTC$	Mc11
			$GA^{m6}ATTC$# [b]	Ba5
RsrII	CGGWCCG	?	$^{m5}CGGWCCG$	Mc11,Qi3
			$CGGW^{m5}CCG$	
			$CGGWC^{m5}CG$	
SacI	GAGCTC	$G^{m6}AGCTC$	$GAG^{m5}CTC$	Mc11
SacII	CCGCGG	?	$^{m5}CCGCGG$	Kl1,Ne2
SalI	GTCGAC	$GTCGA^{m5}C$	$GT^{m5}CGAC$	Br8,Eh2,Lu2,Qi1
			$GTCG^{m6}AC$#	Mc3,Ro4,Ro5,Va4
SalDI	TCGCGA	$TCGCG^{m6}A$	$T^{m5}CGCGA$	Mc13,Ne1,Qi3
Sau3AI	GATC [b]	$G^{m6}ATC$	$GAT^{m5}C$# [b]	Dr1,Eh2,Ja3,Mc3,Ro3,Se1
			$GAT^{m4}C$	Ne5
			$GAT^{hm5}C$	Hu1
Sau96I	GGNCC	?	$GGN^{m5}CC$#	Ko3,Ne2,Pe1
			$GGNC^{m5}C$	
			$GGN^{hm5}C^{hm5}C$	Hu1
Sbo13I	TCGCGA	$TCGCG^{m6}A$	$T^{m5}CGCGA$	Mc11,Ne1
ScaI	AGTACT	$AGTA^{m5}CT$	?	Wo1
ScrFI	CCNGG	$^{m5}CCNGG$	$C^{m5}CNGG$	Mc11,Ne2
			$C^{m4}CNGG$	Ne1
SfaNI	GATGC	$GATG^{m5}C$	$G^{m6}ATGC$	Mc11,Po4
SfiI	$GGCCN_5GGCC$	$GG^{m5}CCN_5GG^{m5}CC$ [b]	$GGC^{m5}CN_5GGCC$	Mc11,Qi2
		$GGCCN_5GGC^{m5}C$		
SflI	CTGCAG	?	$CTGC^{m6}AG$	Br8

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
SgrAI	CRCCGGYG	?	CRC^{m5}CGGYG	Ta3
SinI	GGWCC	?	GGW^{m5}CC#	Ka5,Ka6
SmaI	CCCGGG	C^{m5}CCGGG	^{m4}CCCGGG	Br8,Bu6,Eh2,Ga4
			^{m5}CCCGGG [b]	Ja3,Ka7,Mc3,Qu1
			C^{m4}CCGGG [b]	
			CC^{m4}CGGG	
			CC^{m5}CGGG [b]	
SnaBI	TACGTA	?	TA^{m5}CGTA	Fo1
SnoI	GTGCAC	?	GTG^{m5}CA^{m5}C	Ho2,Wo1
SpeI	ACTAGT	?	^{m6}ACTAGT	Ho1
			A^{m5}CTAGT	Wo1
SphI	GCATGC	GCATG^{m5}C	GC^{m6}ATGC	Mc11,Ne2,Mo3
		G^{hm5}CATG^{hm5}C		
SplI	CGTACG	CGT^{m6}ACG	?	Ne4,Qi3
SpoI	TCGCGA	TCGCG^{m6}A	T^{m5}CGCGA	Ne1,Ne4
			TCG^{m5}CGA	
SsoII	CCNGG	?	C^{m5}CNGG	Vi1
			^{m5}CCNGG	Gr3
Sso47I	GAATTC	?	G^{m6}AATTC#	Ni4
SspI	AATATT	^{m6}AATATT	?	Ne1
SstI	GAGCTC	?	GAG^{m5}CTC	Br8,Ro1
			GAG^{hm5}CT^{hm5}C	Hu1
StuI	AGGCCT	?	AGG^{m5}CCT	Ca4,Mc11
			AGGC^{m5}CT	So3
			AGGC^{m4}CT	Ne1
StySBI	GAGN_6RTAYG [b]	?	G^{m6}AGN_6R^{m}TAYG# [b]	Na1,Na2
StySPI	AACN_6GTRC [b]	?	A^{m6}ACN_6G^{m}TRC# [b]	Na1,Na2
TaqI	TCGA	T^{m5}CGA [b]	TCG^{m6}A#	Gr4,Hu1,Mc3,Va3
		T^{hm5}CGA [b]		Hu1
TaqII	GACCGA	?	G^{m6}ACCGA	Ne4
	CACCCA			
TaqXI	CCWGG	^{m5}CCWGG	?	Gr1
		C^{m5}CWGG		
TfiI	GAWTC	GAWT^{m5}C	?	Fo1
TflI	TCGA	?	TCG^{m6}A	Sa3,Va6
ThaI	CGCG	^{m5}CGCG	^{m5}CGCG	Ga1,Ne1
			^{hm5}CG^{hm5}CG	Hu1
TthHBI	TCGA	T^{m5}CGA	TCG^{m6}A#	Sa3
XbaI	TCTAGA	?	TCTAG^{m6}A#	Mc13,We1
			T^{m5}CTAGA	Gr4,Hu1,Ne2
			T^{hm5}CTAGA	

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
XhoI	CTCGAG [b]	?	CT^{m5}CGAG CTCG^{m6}AG ^{m5}CTCGAG	Br8,Eh2,Eh3,Ka7 Mc3,Va3
XhoII	RGATCY	RG^{m6}ATCY	RGAT^{m5}CY [b]	Br8
XmaI	CCCGGG	CC^{m5}CGGG [b]	^{m4}CCCGGG ^{m5}CCCGGG C^{m4}CCGGG CC^{m4}CGGG	Bu6,Yo5,Yo6
XmaIII	CGGCCG	?	CGG^{m5}CCG	Ne2,Tr2
XmnI	GAAN$_4$TTC	GA^{m6}AN$_4$TTC	G^{m6}AAN$_4$TTC GAAN$_4$TT^{m5}C [b]	Mc11,Ne2
XorII	CGATCG	CG^{m6}ATCG	CGAT^{m5}CG hm5CGAT^{hm5}CG	Br8,Eh2 Hu1

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 (Sm2) and (Co4).

b. *Acc*I nicking occurs slowly in the unmethylated strand of the hemi-methylated sequence GTMKA^{m5}C.

*Afl*I cuts slowly at GGWC^{m4}C.

*Aha*II (GRCGYC) will cut GRCGCC *faster* if these sites are methylated at GRCG^{m5}CC (Ne5), but will not cut GRCGY^{m5}C sites (Ne2,Ne5).

*Asp*718I cuts M·*Cvi*QI -modified (GT^{m6}AC) *Chlorella* virus NY2A DNA. *Asp*718I does not cut GGTAC^{m5}CWGG overlapping *dcm* sites (Mu1) or ^{m5}C-substituted phage XP12 DNA, whereas *Kpn*I cuts XP12 readily (Ne4).

*Ava*I nicking occurs slowly in the unmethylated strand of the hemi-methylated sequence CTCG^{m6}AG/CTCGAG (Ne5).

*Ava*II cuts slowly at GGWC^{m4}C.

Bacillus species have been surveyed for G^{m6}ATC and C^{m5}CWGG specific methylases. Many species have G^{m6}ATC specific methylases but none had C^{m5}CWGG specific methylases (Di3).

*Bal*I sites overlapping *dcm* sites (TGGC^{m5}CAGG) are 50-fold slower than unmethylated sites (Gi1).

*Ban*I gives various rate effects when its recognition sequence is ^{m4}C- or ^{m5}C-methylated at different positions.

*Bgl*I cleavage rate at certain GC^{m5}CN$_5$GGC, GC^{m4}CN$_5$GGC, and GCCN$_5$GG^{m5}C hemi-methylated sites is extremely slow. However, ^{m5}C bi-methylated M·*Hae*III−*Bgl*I sites are completely refractory to *Bgl*I (Ko3,Ne2).

*Bss*HII does not cut M·*Hha*I-modified DNA, in which two different cytosine positions are hemi-methylated, G^{m5}CGCGC/GCG^{m5}CGC (Ne4).

M·*Bst*I modifies the internal cytosine GGAT^{m}CC, but it is not known whether this modification is ^{m5}C or ^{m4}C (Le2).

*Bst*EII cuts the fully ^{m5}C-substituted phage XP12 DNA (Ne5).

*Bst*NI cuts C^{m5}CWGG, ^{m5}CCWGG and ^{m5}C^{m5}CWGG (Ne5). *Bst*NI isoschizomers that are insensitive to C^{m5}CWGG include *Aor*I, *Apy*I, *Bsp*NI, *Mva*I and *Taq*XI (Mc4).

*Bsu*RI nicking occurs in the unmethylated strand of the hemi-methylated sequence GG^{m5}CC/GGCC.

*Cfr*9I, see reference Bu6 for rate effects.

M·*Cre*I is from the unicellular eukaryote *Chlamydomonas reinhardi* (Sa2).

*Dpn*I requires adenine methylation on both DNA strands. Isoschizomers of *Dpn*I include *Cfu*I, *Nan*II, *Nmu*EI, *Nmu*DI and *Nsu*DI (Ca1). *Dpn*I cuts *dam* modified XP12 DNA (Ne6).

M·*Eco dam* modifies GAT^{m5}C at a reduced rate (Ne5). Many other bacteria that modify their DNA at G^{m6}ATC are listed in references Ba1 and Lo1.

*Eco*A, *Eco*B, *Eco*D, *Eco*DXXI, *Eco*K are Type I restriction endonucleases. ^{m}T represents a 6-methyladenine in the complementary strand.

*Eco*PI is a Type III restriction endonuclease (Ba2,Ba1,Ha2).

*Eco*P15 is a Type III restriction endonuclease (Hu2).

*Eco*RI cannot cut hemi-methylated G^{m6}AATTC/GAATTC sites. Bimethylated GA^{m6}ATTC/GA^{m6}ATTC sites are not cut by *Eco*RI or *Rsr*I (Ne5). *Eco*RI shows a reduced rate of cleavage at hemi-methylated GAATT^{m5}C (Tr1) and does not cut an oligonucleotide that contains GAATT^{m5}C in both strands (Br1).

*Eco*RII isoschizomers that are sensitive to C^{m5}CWGG include *Atu*BI, *Atu*II, *Bst*GII, *Bin*SI, *Cfr*5I, *Cfr*II I, *Ecl*II, *Eca*II, *Eco*27I, *Eco*38I and *Mph*I (Ro3). *Eco*RII shows reduced rate of cleavage at hemi-methylated ^{m5}CCWGG/CCWGG sites (Yo1).

*Eco*RV cuts the fully ^{m5}C-substituted phage XP12 DNA (Ne5).

*Eco*R124 and *Eco*R124/3 are Type I restriction endonucleases. ^{m}T represents a 6-methyladenine in the complementary strand.

is a Type I restriction endonuclease.

*Fok*I cuts about two-fold to four-fold more slowly at CATC^{m5}C than at unmodified sites (Ne5).

M·*Fok*I in ref Po3 corresponds to M·*Fok*IA in ref Po4.

*Hae*II show a reduction in rate of cleavage when its recognition sequence is modified at RGCG^{m5}CY.

*Hae*III nicking occurs in the unmethylated strand of the hemi-methylated sequence GG^{m5}CC/GGCC.

*Hinf*I 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. *Hinf*I does cut phage XP12 DNA, although at a reduced rate (Gr4,Ne5). *Hinf*I 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 *Hinf*I sites is only about ten-fold (Hu1,Ne5,Pe1).

*Hpa*II nicking in the unmethylated strand of the hemi-methylated sequence ^{m5}CCGG/CCGG is in dispute (Be3,Bu6,Ko3). HpaII cuts hemimethylated mCCGG 50 times slower and fully methylated mCCGG 3000 times slower than unmethylated DNA (Ko3). See reference (Bu6) for *Hpa*II rate effects.

*Kpn*I sensitivity to hemi-methylated GGTA^{m5}CC and GGTAC^{m5}C sites has been reported. *Kpn*I efficiently cuts ^{m5}C-substituted phage XP12 DNA, but not *Chlorella* virus NY2A DNA, which carries both GT^{m6}AC and ^{m5}CC modifications (Ne4).

*Mae*II nicks slowly in the unmethylated strand of hemi-methylated A^{m5}CGT/ACGT (Mo2).

*Mbo*I isoschizomers that are sensitive to G^{m6}ATC include *Bss*GII, *Bsa*PI, *Bsp*74I, *Bsp*76I, *Bsp*105I, *Bst*XII, *Bst*EIII,*Bss*GII, *Cpa*I, *Cty*I, *Cvi*AI, *Cvi*BII, *Cvi*HI, *Dpn*II, *Fnu*AII, *Fnu*CI, HacI, MeuI, MkrAI, *Mme*II, *Mno*III, *Mos*I, Msp67II, MthI, MthAI, *Nde*II, *Nfl*AII, *Nfl*BI, *Nfl*I, *Nla*DI *Nla*II, *Nme*CI, *Nph*I, *Nsi*AI, *Nsp*AI, *Nsu*I, *Pfa*I, *Rlu*1I, *Sal*AI, *Sal*HI, *Sau*6782I, *Sin*MI, *Tru*II (Ro3).

*Mbo*II cuts the fully ^{m5}C-substituted phage XP12 DNA (Ne5), although certain hemi-methylated ^{m5}C-containing substrates are reported not to be cut (Gr4).

*Mfl*I cuts slowly at ^{m6}AGATCY sites (On1).

Mammalian methylase is the ^{m5}CG methyltransferase from *Mus musculus.* (mouse) (Be6).

*Msp*I cuts the hemi-methylated sequence C^{m5}CGG/CCGG (Wa5) and C^{m4}CGG/CCGG duplexes (Bu6). *Msp*I cuts very slowly at GGC^{m5}CGG (Bu2,Ke1). An M·*Msp*I clone methylates ^{m5}CCGG (Wa5,Wa2). However, there is a report that *Moraxella sp.* chromosomal DNA is methylated at ^{m5}C^{m5}CGG (Je2).

*Mva*I nicking occurs in the unmethylated strand of the hemi-methylated sequence ^{m4}CCWGG/CCWGG and CC^{m6}AGG/CCTGG (Ku3). *Mva*I cuts XP12 DNA very slowly at ^{m5}C^{m5}CWGG.

*Nan*II requires adenine methylation on both DNA strands (Ca1). *Nan*II cuts M·*Eco dam* modified XP12 DNA (Ne5).

*Nci*I may cut ^{m5}C^{m5}CGG methylated DNA (Br8,Je2). Possibly the second methylation negates the effect of C^{m5}CGG.

*Nco*I is blocked by M·*Sec*I (CCNNGG) (Ne5).

*Ncr*I is a *Bgl*II isoschizomer from *Nocardia carnia* Beijing (Qi1).

*Nde*I cuts the fully ^{m5}C-substituted phage XP12 DNA (Ne5).

*Nde*II cuts the fully ^{m5}C-substituted phage XP12 DNA (Ne5).

Ngo. There is some confusion about naming restriction enzymes from these strains. NgoPII, NgoII and NgoSI may be the same. NgoPIII may be NgoIII.

*Ngo*PII does not cut overlapping dcm sites (Su4).

*Nmu*DI requires adenine methylation on both DNA strands (Ca1).

*Nmu*EI requires adenine methylation on both DNA strands (Ca1).

*Pae*RI cuts hemimethylated CT^{m5}CGAG/CTCGAG sites 100 fold slower and cuts fully methylated CT^{m5}CGAG/CT^{m5}CGAG 2900 fold slower than unmethylated sites (Gh1). Hemi- or full methylation at ^{m6}A completely protects against PaeR7 cleavage (Gh1).

*Rsa*I cuts the fully ^{m5}C-substituted phage XP12 DNA (Ne5), but does not cut *Chlorella* virus NY2A DNA, which is modified at GT^{m6}AC (Ne4,Xi1). DNA from *Rhodopseudomonas sphaeroides* species Kaplan is cut by *Asp*718I, but not by *Rsa*I or *Kpn*I (Ne4). It is likely that M·*Rsa*I specifies GTA^{m4}C; and high levels of ^{m4}C are present in *R. sphaeroides* DNA (Eh3).

*Rsr*I cannot cut hemi-methylated G^{m6}AATTC/GAATTC sites.

*Sau*3AI nicking occurs in the unmethylated strand of the hemi-methylated sequence GAT^{m5}C/GATC (St3). *Sau*3AI cuts at a reduced rate at ^{m6}AGATC (On1). *Sau*3AI isoschizomers that are insensitive to G^{m6}ATC include *Bce*243I, *Bsp*49I, *Bsp*51I, *Bsp*52I,*Bsp*54I, *Bsp*57I, *Bsp*58I, *Bsp*59I,*Bsp*60I, *Bsp*61I, *Bsp*64I, *Bsp*65I, *Bsp*66I, *Bsp*67I, *Bsp*72I, *Bsp*AI, *Bsp*91I, *Bsr*PII, *Cpf*I, *Csp*5I, *Cpe*I, *Fnu*EI, *Msp*BI, *Sau*CI, *Sau*DI, *Sau*EI, *Sau*FI, *Sau*GI and *Sau*MI (Ro3).

*Sfi*I cannot cut M·*Bgl*I-modified DNA (Ne1).

*Sma*I nicking occurs in the unmethylated strand of the hemi-methylated sequence CC^{m5}CGGG/CCCGGG (Bu6,Wa5). *Sma*I may cut C^{m5}C^{m5}CGGG methylated DNA (Br8,Je2) Possibly the second methylation negates the effect of CC^{m5}CGGG. There are conflicting results regarding *Sma*I: ^{m5}CCCGGG is not cut when modified by M·*Aqu*I methyltransferase (Ka7) or at overlapping M·*Hae*III-*Sma*I sites (GG^{m5}CCCGGG, Ne5). Other investigators have reported that *Sma*I cuts at a reduced rate at hemi-methylated ^{m5}CCCGGG sites (Bu6).

*Spl*I cuts GT^{m6}AC-modified *Chlorella* virus NY2A DNA, but does not cut *Kpn*I-digested XP12 DNA (Ne4).

*Sty*SBI and *Sty*SPI are Type I restriction endonucleases. ^{m}T represents a 6-methyladenine in the complementary strand.

*Taq*I cuts very slowly at T^{hm5}CGA (Hu1). *Taq*I cuts the fully ^{m5}C substituted phage XP12 DNA (Hu1,Ne5).

M·*Taq*I methylates T^{m5}CGA at least 20 fold slower that unmodified TCGA (Mc7).

*Xba*I 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.

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

*Xma*I is claimed not cut CC^{m5}CGGG in one report (Br8). See reference Bu6 for rate effects.

*Xmn*I cuts the fully ^{m5}C substituted phage XP12 DNA (Ne5). *Xmn*I cuts slowly at some sites in DNA methylated on *both* strands at GAAN$_4$TT^{m5}C (Ne5).

TABLE II: DNA methyltransferases and their modification specificities
Cloned methylases in bold.

Methylase [a]	Specificity [a]	References
M·AatII	GACGTC	Lu2
M·AccI	GTMK^{m6}AC	Lu2
M·AflII	CTTAAG (^{m6}A)	Lu2
M·AlaK21	GAT^{m5}C	Sl1
M·AluI	AG^{m5}CT	Kr2,Lu2
M·Alw26I	GT^{m5}CTC	Bu4
	and G^{m6}AGAC	Bu4
M·ApaI	GGG^{m5}CCC	Mc8,Tr2
M·AquI	^{m5}CYCGRG	Ka7,Ka8
M·AseI	ATTAAT	Mo3
M·AseII	CCSGG	Mo3
M·AvaI	CYCGRG	Lu2
M·AvaII	GGWCC	Lu2
M·AvrI	CYCGRG	Lu3
M·BalI	TGG^{m5}CCA	Lu2,Mc8
Bacillus	G^{m6}ATC [b]	Di3
M·BamHI	GGAT^{m4}CC	Ha1,Lu2,Na3
M·BamHII	G^{m}CWGC?	Ha1
M·BanI	GGYRCC	Lu2
M·BanII	GRGCYC	Lu2
M·BbvI	G^{m5}CWGC	Do1,Ha1,Va5
M·BbvSI	G^{m}CWGC	Ha1,Va5
M·Bbv	G^{m6}AT	Ha1
M·Bbv	A^{m6}AG	Ha1
M·BcnI	C^{m4}CSGG	Ja4,Ja6,Ja7,Pe2,Po6
M·BepI	^{m5}CGCG	Ku2
M·BglI	GCCN5GGC (^{m4}C)	Lu2
M.Bme216I	GGWC^{m}C	Ma9
M·BnaI	GGAT^{m}CC	Ki1
M·BspRI	GG^{m5}CC	Fe2,Ko1,Po2,Qi3,Sz4,Ve1
M.Bsp106I	ATCG^{m6}AT	Pa2
M.Bsp6I	GCNCG	Ja3
M·BstI	GGAT^{m}CC	Le2
M·BstVI	CTCG^{m6}AG	Ba7
M·BstYI	RGAT^{m}CY	Va2
M·BsuBI	CTGC^{m6}AG	Xu1
M·BsuEI	^{m5}CGCG	Ga1,Gu7,Ik1,Je1
M·BsuFI	^{m5}CCGG	Gu7,Ik1,Je1,Wa7
M·BsuMI	YT^{m5}CGAR	Gu1,Gu2,Gu7,Je1,Sh1
M·Bsuφ3T	GG^{m5}CC	Be1,Gu5,Gu4,No2,No3
	and G^{m5}CNGC	No1,Tr1

Methylase [a]	Specificity [a]	References
M·Bsup11I	GG^{m5}CC and G^{m5}CNGC	Gu4,Gu5,Gu7,No1,No2
M·Bsup11s	GGCC and GDGCHC	Be1
M·BsuQI	^{m}CCGG	Je2
M·BsuRI	GG^{m5}CC [b]	Gu6,Ki2,Ki3
M·BsuSPβ	GG^{m5}CC and G^{m5}CNGC	Gu4,Gu5,Gu7,Je2,Ki2,N16 No2,Tr1,Tr3
M·BsuSPRI	GG^{m5}CC	Be1,Gu5,Gu7,No2
	and ^{m5}C^{m5}CGG	Po1
	and C^{m5}CWGG	Be2,Bu1,Gu3,Gu5,Ki2,Po1
M·BsuSPR191	^{m5}C^{m5}CGG and C^{m}CWGG	Je2,No2,Po1
M·BsuSPR83I	GG^{m5}CC and C^{m5}CWGG	Gu3
M·CfrA	GCAN$_8$GTGG	Da2,Da3
M·CfrI	YGG^{m5}CCR	Po6
M·Cfr6I	CAG^{m4}CTG	Bu5
M·Cfr9I	C^{m4}CCGGG	Kl3,Po6
M·Cfr10I	R^{m5}CCGGY	Po6
M·Cfr13I	GGN^{m5}CC	Bi5
M·ClaI	ATCG^{m6}AT	Mc3
M·CreI	T^{m5}CR	Sa2 (Chlamydomonas)
M·CtyI	G^{m6}ATC#	Ri2
M·CviBI	G^{m6}ANTC	X2
M·CviBIII	TCG^{m6}A	Na4
M·CviJI	RG^{m5}CY	Sh3
M·CviPI	^{m5}CC	Xi4
M·CviQI	GT^{m6}AC	Xi2,Xi5
M·CviRI	TGC^{m6}A	St1
M·CviRII	GT^{m6}AC	St1
M·DdeI	^{m5}CTNAG	Ho3,Lu2,Sz3
M·DpnII	G^{m6}ATC	De1,La3,La4,La5,Ma6
M·DpnA	?G^{m6}ATC?	De1
M·EaeI	YGG^{m5}CCR	Ja1,Wh1
M·EagI	CGGCCG	Sz2
M·EcaI	GGT^{m6}ACC	Br2
M·Eco dam	G^{m6}ATC	Br6,Bu9,Dr1,Gi2,Ha2,He2,Ur1
M·Eco dcmI	C^{m5}CWGG	Bo5,Ma10,So2,Ur1
M·Eco dcmII	R^{m}CCGG	Bu8,Ne8
M·Eco dcmIII	^{m}CCWGG	Ni2
M·Eco dcmIV	GGWC^{m}C	Mo1,Ni2
M·EcoA	G^{m6}AGN$_7$G^{m}TCA [b]	Co7,Fu2
M·EcoB	TG^{m6}AN$_8$^{m}TGCT [b]	Go3
M·EcoD	TTAN$_7$GTCY [b]	Go3

Methylase [a]	Specificity [a]	References
M·EcoDXXI	TCAN$_7$ATTC [b]	Sk1
M·EcoE	GAGN$_7$ATGC [b]	Fu2
M·EcoK	A^{m6}ACN$_6$G^{m}TGC [b]	Bo2,Go3,Ka1,Lo2,Sa1
M·EcoPI	AG^{m6}ACC [b]	Ba2,Hu2
M·Eco P1 dam	G^{m6}ATC [b]	Co5
M·EcoP15	C^{m6}AGCAG	Hu2
M·EcoRI	GA^{m6}ATTC	Du1,Gr2,Ke2 Ne2,Ne9,Ru1
M·EcoRII	C^{m5}CWGG	Bh1,Bu7,Bu8,Ko6,Ko7,Ko8 Ma10,Sc6,So1,Yo4
M·EcoRV	G^{m6}ATATC	Bo3
M·EcoR124	GAAN$_6$RTCG (^{m6}A)	Pr2,Pr3
M·EcoR124/3	GAAN$_7$RTCG (^{m6}A)	Pr2,Pr3
M·EcoT1 dam	G^{m6}ATC	Sc1,Sc7
M·EcoT2 dam	G^{m6}AT	Br7,Ha2,Ha3,Mi1,Sc4,Sc5
M·EcoT4 dam	G^{m6}ATC	Ha4,Ma1,Mi2,Sc3,Sc4,Sc5
M·Eco31I	GGT^{m5}CTC	Bu4
	and G^{m6}AGACC	Bu4
M·Eco47II	GGNCC	Po6
M·Eco51I	CTGAAG (^{m6}A)	Po6
M·Eco57I	CTGAAG (^{m6}A)	Po6
M·Eco64I	GGYRCC	Po6
M.Eco72I	CACGTG (^{m5}C)	Po6
M·Eco98I	AAGCTT	Po6
M·Eco105I	TACGTA	Po6
M·Esp3I	GGT^{m6}CTC	Ja3
	GAG^{m6}ACC	
M·FnuDI	GGCC (^{m5}C)	Lu2,Va1
M·FnuDII	^{m5}CGCG	Lu2,Ne1
M·FnuDIII	GCGC	Lu2
M·FokI	GG^{m6}ATG	La6,Lo3,Lu2,Ma8,Nw1
	and C^{m6}ATCC	
M·FspI	TGCGCA	Me1
M·FV3	??^{m}C??	Es1 (Frog virus)
M·HaeII	RGCGCY	Lu2,Sl3
M·HaeIII	GG^{m5}CC [b]	Lu2,Ma5,Sl3
M·HapII	C^{m}CGG	Wa1
M·HgaI	GACGC (^{m}C)	Lu2,Nw1
M·HgiAI	GWGCWC	Lu2
M·HgiCI	GGYRC^{m5}C	Er1
M·HgiCII	GGWC^{m5}C	Er1
M·HgiEI	GGWC^{m5}C	Er1
M·HhaI	G^{m5}CGC	Ba9,Ca3,Lu2,Sm1,Wu1,Za1
M·HhaII	G^{m6}ANTC	Ch1,Ke1,Ma3,Ma4,Sc9,Sm1
M·HincII	GTYR^{m6}AC	Gr4,Mc8,Ro7 Re2

Methylase [a]	Specificity [a]	References
M·HindII	GTYR^{m6}AC	Lu2,Re2,Ro6,Ro7
M·HindIII	^{m6}AAGCTT	Lu2,Ro6,Ro7
M·HinfI	G^{m6}ANTC	Ch1,Lu2
M·HinPI	GCGC	Ba9,Lu2
M·HjaI	GATATC (^{m6}A)	Da1
M·HpaI	GTTA^{m6}AC	Br8,Yo3
M·HpaII	C^{m5}CGG	Lu2,Ma5,Qu1,Wi2,Yo2
M·HphI	T^{m5}CACC	Mc8,Ne2,Ne4
M·H2	GGCC GCNGC GDGCHC	La8 (Bacillus phage)
M·Kpn2I	TCCGGA	Po6
M·MboI	G^{m6}ATC	Mc8
M·MboII	GAAG^{m6}A	Mc12,Ne4,Ne2
Mammals	^{m5}CG [b]	Be6 (Mouse)
M·MspI	^{m5}CCGG [b]	Eh2,Je2,Lu2,Nw2,Wa1,Wa5
M·MstI	TGCGCA	Me1
M·MvaI	C^{m4}CWGG	Kl3,Po6
M·MwoI	GCN$_7$GC (^{m4}C)	Lu2,Lu4
M·NaeI	GCCGGC	Lu2,Va1
Neurospora	??^{m5}C??	Se2
M·NcoI	CCATGG (^{m}C)	Lu2,Va1
M·NdeI	CATATG (^{m6}A)	Si1
M·NgoMVI	GGNNCC [b]	Pi5
M·NgoI	RGCGCY [b]	Ri1
M.NgoPI	RG^{m}CGCY [b]	Su2
M·NgoII	GG^{m5}CC [b]	Ko5,Ri1
M·NgoAI	GG^{m5}CC [b]	Pi3
M.NgoPII	GG^{m5}CC [b]	Su3,Su4
M·NgoIII	CCGCGG [b]	Ko5,Ri1
M·NgoIV	G^{m5}CCGGC [b]	Ch2,Ko15,Ri1
M·NgoV	GGNN^{m5}CC [b]	Ko5,Pi2
M·NgoVI	G^{m6}ATC [b]	Ko5
M·Ngo VII	G^{m}CWGC [b]	Ko5
M·NgoBI	T^{m5}CACC [b]	Pi3
M·NgoBII	GTAN$_5$^{m5}CTC [b]	Pi3
M·NlaI	GGCC	Mo3
M·NlaIII	C^{m6}ATG	La1,Lu2,Mo3
M·NlaIV	G^{m5}CCGGC	Lu2
M·NlaV	GGNN^{m5} CC	Mo3
M·NlaX	??^{m}C??	La1
M·PaeR7I	CTCG^{m6}AG	Gi3,Th1,Th2
M·PstI	CTGC^{m6}AG	Le1,Wa3,Wa4,Wa6
M·PvuII	CAG^{m4}CTG	Bl1,Ta2
M·Rrh4273I	GTCG^{m6}AC	Ba6

Methylase [a]	Specificity [a]	References
M·RsrI	GA^{m6}ATTC	Ba5,Ka10
M·SacII	CCGCGG	Lu2
M·SalI	GTCG^{m6}AC	Lu2,Ro4,Ro5
M·Sau3A	GAT^{m5}C	Se1
M·Sau96I	GGN^{m5}CC	Lu2,Ne1,Sz1
M·SfiI	GGCCN5GGCC (^{m4}C)	Ba8
M·SinI	GGW^{m5}CC	Ka5,Ka6
M·SmaI	CC^{m}CGGG	He1,Po6
M·SphI	GCATGC	Lu2
M·Sso47I	G^{m6}AATTC	Ka9,Bu4
M·Sso47II	C^{m}CNGG	Ka9,Ni1,Ni3
M·SspMQI	^{m5}CG	Nu1,Pi5,Re3
M·StyI	CCWWGG	Re1
M·StySBI	G^{m6}AGN$_6$R^{m}TYG [b]	Fu1,Fu3,Ga3,Na1,Na2
M·StySPI	A^{m6}ACN$_6$G^{m}TRC [b]	Fu1,Fu3,Na1,Na2
M·StySQ	A^{m6}ACN$_6$R^{m}TAYG [b]	Fu1,Fu3
M·StySJ	G^{m6}AGN$_6$G^{m}TRC [b]	Ga3
M·TaqI	TCG^{m6}A	Lu2,Mc3,Sa3,Sl2
M·TthHBI	TCG^{m6}A	Mc3,Sa3
M·TflI	TCG^{m6}A	Sa3,Va6
Tetrahymena	??^{m6}A??	Ca2,Go1
M·XbaI	TCTAG^{m6}A	Lu2,Mc13,Va1
M·XmaI	CCCGGG (^{m4}C)	Ba8
M·XmaIII	CGG^{m}CCG	Mc8,Tr2
M·XmnI	GAAN$_4$TTC	Fe1

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]	References
M·AluI ($AG^{m5}CT$)		$AG^{m4}CT$	Bu5
M·BamHI ($GGAT^{m4}CC$)	$GG^{m6}ATCC$	$GGATC^{m5}C$	La7,Mc10
M·BstI ($GGAT^{m}CC$)[c]	$GG^{m6}ATCC$		Le2
M·Cfr6I ($CAG^{m4}CTG$)		$CAG^{m5}CTG$	Bu5
M·ClaI ($ATCG^{m6}AT$)	$^{m6}ATCGAT$		M9,Mc11,We1
	$AT^{m5}CGAT$		
M·CviBIII ($TCG^{m6}A$)	$T^{m5}CGA$		Mc10,Va4
M·EcoRI ($GA^{m6}ATTC$)	$GAATT^{m5}C$	$G^{m6}AATTC$	Br2
M·EcoRII ($C^{m5}CWGG$)		$C^{m4}CWGG$	Bu4
M·Eco dam ($G^{m6}ATC$)	$GAT^{m5}C$ [c]		Mc10
	$GAT^{hm5}C$		
	$GAT^{m4}C$		Ne4
M·FokIA ($GG^{m6}ATG$)[c]	$CATC^{m5}C$	$CAT^{m5}CC$	Po3,Po4,Sc2
M·HhaI ($G^{m5}CGC$)	$GCG^{m5}C$		Ro1
M·HhaII ($G^{m6}ANTC$)	$GANT^{m5}C$		Mc10
M·HpaII ($C^{m5}CGG$)		$^{m5}CCGG$	Mc9,Mc10
M·HphI ($T^{m5}CACC$)	$GGTG^{m6}A$		Mc10
M·MboI ($G^{m6}ATC$)	$GAT^{m5}C$		Mc10
M·MboII ($GAAG^{m6}A$)	$T^{m5}CTT^{m5}C$		Mc10
M·MspI ($^{m5}CCGG$)		$C^{m5}CGG$	Mc10
M·MvaI ($C^{m4}CWGG$)	$C^{m5}CWGG$		Bu4
	$^{m5}C^{m5}CWGG$		Ne1
M·PvuII ($CAG^{m4}CTG$)		$CAG^{m5}CTG$	Bu5
M·EcoT2 dam ($G^{m6}ATY$)	$GAT^{hm5}C$		Do2,Mi1
M·EcoT4 dam ($G^{m6}ATC$)	$GAT^{hm5}C$		Sc4
M·TaqI ($TCG^{m6}A$)		$T^{m5}CGA$ [c]	Mc7

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/isomethylator pairs that differ in their sensitivity to sequence-specific methylation.

	Restriction isoschizomer pairs [a,b]		
Methylated sequence [c]	Cut by	Not cut by	References
^{m4}CCGG	MspI	HpaII	Ne1
C^{m5}CGG	MspI	HpaII (HapII)	Eh2,Mc11
C^{m4}CGG	MspI	HpaII	Bu6
CC^{m5}CGGG	XmaI (Cfr9I)	SmaI	Bu6
C^{m5}CWGG	BstNI (MvaI)	EcoRII	Bu4
G^{m6}ATC	Sau3A (FnuEI)	MboI (NdeII)	Ge1,Lu1,Mc9,Ro3
GAT^{m5}C	MboI	Sau3A	Ne4
GAT^{m4}C	MboI	Sau3A	Ne4
GGC^{m5}C	HaeIII	NgoPII	Su4
GGTAC^{m5}C	KpnI	Asp718I	Mu1
GGTA^{m5}C^{m5}C	KpnI	Asp718I	Ne4
GGWC^{m5}C	AflI	AvaII (Eco47I)	B3,Ja5,Wh2
RG^{m6}ATCY	XhoII (BstYI)	MflI	Mc9,Ne4
T^{m5}CCGGA	AccIII	BspMII (MroI)	La2,Sc2
TC^{m5}CGGA	AccIII	BspMII (MroI)	Sc2
TCCGG^{m6}A	BspMII (MroI)	AccIII	Ke3,Ne4
TCGCG^{m6}A	Sbo13I (SalDI)	NruI	Mc11,Ne4
TT^{m5}CGAA	AsuII	Csp45I	Sc10
CGGWC^{m5}CG	CspI	RsrII	Qi3

	Restriction isomethylator pairs [d,e]		
Methylated sequence [c]	methylated by	Not methylated by	References
T^{m5}CGA	M.CviBIII (TCG^{m6}A)	M·TaqI	We2

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. 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.
c. See footnote "a" of Table I.
d. In each row the first column lists a methylated sequence, the second column lists an isomethylator that modifies this sequence, and the third column lists an isomethylator that does not modify this sequence.
e. An enzyme is classified as insensitive to methylation if it modifies the methylated sequence at a rate that is at least one tenth the rate at which it modifies 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.[a]

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

CC	Cvi NY
RGCY	CviJI
CATG	NlaIII
CCTC	MnlI
AGCT	AluI
CCGG	BsuFI, BsuQI, HapII, HpaII, MspI
CGCG	AccII, BepI, BstUI, BsuEII, FnuDII, ThaI
$G^{m6}ATC$	DpnI, NanII, NmuDI, NmuEI
GATC	Bce243I, BsaPI, Bsp67I, BspAI, BspPII, BsrPII, BssGII, BstEIII, BstXII, CpaI, CtyI, CviAI, DpnII, FnuAII, FnuCI, FnuEI, MboI, MmeII, MnoIII, MosI, MthI, NdeII, NflI, NlaII, NsiAI, NsuI, PfaI, Sau3A, SinMI
GCGC	HhaI, HinPI
GGCC	BsuRI, HaeIII, NgoPII
GTAC	CviQI, RsaI
TCGA	TaqI, TflI, TthI
TTAA	MseI
CCNGG	ScrFI
CTNAG	DdeI
GANTC	CviBI, HhaII, HinfI
GGNCC	Cfr13I, Sau96I
CCWGG	AacI, AorI, ApyI, AtuBI, AtuII, BinSI, BspNI, BstGII, BstNI, Cfr5I, CfrII I, EcaII, EclII, EcoRII, Eco27I, Eco38I, MphI, MvaI, TaqXI
CCSGG	BcnI, NciI
GCAGC	BbvI
GGWCC	AvaII, Bme216I, Eco47I, HgiCII, HgiEI, SinI
AGACC	EcoPI
ACCTGC	BspMI
CAGCAG	EcoP15
CATCC	FokI
GAAGA	MboII, NcuI
GAAGAG	EarI
GAATGC	BsmI
GACCGA and CACCCA	TaqII
GACGC	HgaI
GATGC	SfaNI
GGATC	AlwI, BinI
GTCTC	BsmAI
TCACC	HphI, NgoBI
GDGCHC	Bsp1286I
CYCGRG	AquI, AvaI
GRCGYC	AhaII
GRCGYC	AosII, BbiII, BanII
GRGCYC	HgiJII
GTMKAC	AccI
GTYRAC	HinCII

GWGCWC	HgiAI
RCCGGY	Cfr10
RGCGCY	HaeII, NgoPI
RGATCY	BstYI, MflI, XhoII
YGGCCR	CfrI, EaeI
RGGNCCY	DraII
AAGCTT	HindIII
ACGCGT	MluI
ACTAGT	SpeI
AGATCT	BglII, NcrI
AGCGCT	AviII, Eco47III
AGGCCT	StuI
ATCGAT	BanIII, BspXI, ClaI
ATGCAT	NsiI
CAGCTG	Cfr6I, PvuII
CATATG	NdeI
CCATGG	NcoI
CCCGGG	Cfr9I, SmaI, XmaI
CCGCGG	SacII
CGATCG	BmaDI, PvuI, RshI, XorII
CGGCCG	EagI, XmaIII
CGTACG	PfuI, SplI
CTCGAG	BsuMI, BsuRII, PaeR7I, XhoI
CTGCAG	BsuBI, PstI, SflI
CTTAAG	AflII
GAATTC	EcoRI, RsrI, Sso47I
GACGTC	AatII
GAGCTC	SacI, SstI
GATATC	EcoRV
GCATGC	SphI
GCCGGC	Mlu9273II, NaeI
GCGCGC	BssHII
GCTAGC	NheI
GGATCC	BamHI, BamFI, BamKI, BamNI, BstI, BstI, Bst1503I
GGCGCC	BbeI, NarI
GGTACC	Asp718I, KpnI
GGGCCC	ApaI
GTCGAC	Rrh4273I, SalI
GTGCAC	ApaLI
GTTAAC	HpaI
TCATGA	BspHI, RspXI
TCCGGA	AccIII, BspMII, Kpn2I, MroI
TCGCGA	AmaI, MluI9273I
TCGCGA	NruI, SalDI, Sbo13I, SpoI
TCTAGA	XbaI
TGATCA	AtuCI, BclI, BspXII, BstGI, CpeI
TGCGCA	FspI
TGGCCA	BalI
TTCGAA	AsuII, BstBI, Csp45I
TTTAAA	DraI
$CCAN_6TGG$	PflMI, BstXI
CCTNAGG	MstII
$GAAN_4TTC$	XmnI
$GATN_4ATC$	MamI
$GCCN_5GGC$	BglI

GCTNAGC	EspI
GGTNACC	BstEII, EcaI
CGGWCCG	CspI, RsrII
$GAAN_6RTCG$	EcoR124
$GAAN_7RTCG$	EcoR124/3
$AACN_6GTGC$	EcoK
$AACN_6GTRC$	StySPI
$GAGN_7ATGC$	EcoE
$GAGN_7GTCA$	EcoA
$GAGN_6RTAYG$	StySBI
$TCAN_7ATTC$	EcoDXXI
$TGAN_8TGCT$	EcoB
$TTAN_7GTCY$	EcoD
CRGCGGYG	SgrAI
GGCCGGCC	FseI
GCGGCCGC	NotI
$GGCCN_5GGCC$	SfiI