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 m^4C , m^5C , hm^5C , and m^6A , 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 m^4C , m^5C , hm^5C , and m^6A 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 m^5CG and m^5CNG 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 m^5CG and m^5CNG are useful for digestion of plant DNA which is frequently methylated at these positions. Endonucleases that are unaffected by these two cytosine modifications include: *AccIII*, *AflIII*, *AhaIII*, *AseI*, *Asp700I*, *AsuII*, *BbuI*, *BclI*, *BspHI*, *BspNI*, *BstEII*, *BstNI*, *CviQI*, *DpnI*, *DraI*, *EcoRV*, *HinCII*, *HpaI*, *KpnI*, *MboII*, *MseI*, *NdeI*, *NdeII*, *PacI*, *RsaI*, *RspXI*, *SpeI*, *SphI*, *SspI*, *SwaI*, *TaqI*, *TthHBI* and *XmnI*.

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 m^5CpG modification at overlapping sites, including *AatII*, *ApeI*, *AviII*, *BbeI*, *BmaDI*, *BssHII*, *BspMII*, *BstBI*, *Clal*, *CspI*, *Csp45I*, *EagI*, *EclXI*, *Eco47III*, *FseI*, *FspI*, *Kpn2I*, *MluI*, *Mlu9273I*, *Mlu9273II*, *MroI*, *NaeI*, *NarI*, *NotI*, *NruI*, *PfuI*, *PmlI*, *PpuAI*, *PvuI*, *RsrII*, *SalI*, *SalDI*, *Sbo13I*, *SfiI*, *SmaI*, *SnaBI*, *SplI*, *SpoI*, *XhoI* and *XorII* (see **Table I**).

Only four enzymes suitable for pulsed field mapping of eukaryotic chromosomes are known to cut m^5CG -modified DNA: *AccIII*, *AsuII*, *Cfr9I* and *XmaI*. It has been determined that *SfiI* is sensitive to m^5C modification at the second cytosine of its recognition sequence, $GGC^m^5CN_5GGCC$. *SfiI* is therefore

sensitive to overlapping m^5CG methylation at $GGC^m^5CGN_4GGCC$ sites in mammals and overlapping *dcm* methylation at $GGC^m^5CWGGNNGGCC$ sequences in *E. coli*.

m^4C and m^5C Cytosine modifications

In some cases, a restriction enzyme may differ with to sensitivity to m^4C and m^5C at a particular sequence. For example, *BstNI* and *MvaI* cut m^5C , but not m^4C modified CCWGG sequences. *KpnI* cuts $GGTAC^m^5C$ but not $GGTAC^m^4C$. *BstYI* cuts $RG-AT^m^5CY$ but not $RGAT^m^4CY$. Restriction enzymes we have tested for sensitivity to m^4C include: *AatI*, *AflI*, *AlwI*, *AvaII*, *BanI*, *BglI*, *BstI*, *BstNI*, *BstYI*, *DpnI*, *FokI*, *MboI*, *MvaI*, *NarI*, *NciI*, *PflMI*, *Sau3A*, and *ScrFI*.

Rate of cleavage at methylated restriction sites

m^4C , m^5C , hm^5C , and m^6A 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. BamHI* methylase modifies $GGAT^m^4CC$; and *BamHI* 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, *BamHI* cuts DNA which has been modified at $GGATC^m^4C$ or $GGATC^m^5C$, but cannot cut DNA methylated at $GGAT^m^5CC$.

(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, *NarI* does not cut at overlapping *M. MvaI-NarI* $GGCGCC^m^4CCWGG$ sites (Ne1); and *HaeIII* cannot cut certain $GGCC^m^T$ sites, where m^T are modified 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^mC, but methylates GAT^mC 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 *DpnI* to create cleavages at eight- to twelve-base-pair sequences (Mc6, Mc12). *M·ClaI* and *DpnI* 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·XbaI/DpnI* 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·FnuDII/NotI* 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·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, CCGG-ATCCGG (Mc10).

Polypyrimidine oligonucleotides have been used in DNA triplexes to selectively mask restriction-modification sites. For example, polypyrimidine triplexes which overlap *M·TaqI* 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* (^m6A), *mcrA* (^m5CG), *mcrB* (^m5C) (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 ^m5CpG is restricted by *mcrA* (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
<u>AacI</u>	CCWGG	C ^{m5} CWGG	?	Br8
<u>AatI</u>	AGGCCT	?	AGG ^{m5} CCT	Ne1
			AGGC ^{m5} CT	So3
			AGGC ^{m4} CT	Ne1
<u>AatII</u>	GACGTC	?	GACGT ^{m5} C	Ne1
			GAm ⁵ CGTC	Fo1
<u>AccI</u>	GTMKAC	?	GTMK ^{m6} AC [#]	Lu2,Mc3
			GTMKA ^{m5} C	
<u>AccII</u>	CGCG	?	^{m5} CGCG	Ga2
<u>AccIII</u>	TCCGGA	T ^{m5} CCGGA	TCCGG ^{m6} A	Ke3,La2,Sc2
		TC ^{m5} CGGA		
<u>AflI</u>	GGWCC	GGWC ^{m5} C ??	?	Mc11,Wh2
		GGWC ^{m4} C		
<u>AflII</u>	CTTAAG	?	^{m5} CTTAAG	Ne1
			CTTA ^{m6} AG	
<u>AflIII</u>	ACRYGT	?	A ^{m5} CRYGT	Ne1
<u>AhaII</u>	GRCGYC ^b	?	GR ^{m5} CGYC	Ka2,Hu1
			GRCGY ^{m5} C	
<u>AluI</u>	AGCT	?	^{m6} AGCT	Gr4,Mc11,Ne2
			AG ^{m4} CT	
			AG ^{m5} CT [#]	Hu1,Wo1
			AG ^{hm5} CT	Bu5
<u>AlwI</u>	GGATC	?	GG ^{m6} ATC	Ne4
			GGAT ^{m4} C	
<u>AmaI</u>	TCGCGA	TCGCG ^{m6} A	?	Mc13
<u>AosII</u>	GRCGYC	?	GR ^{m5} CGYC	Eh2,Gr4,Va3
<u>ApaI</u>	GGGCCC	?	GGG ^{m5} CCC [#]	La9,Tr2
			GGGCC ^{m5} C	
<u>ApeI</u>	ACGCGT	?	A ^{m5} CGCGT	Ne1,Qi2
<u>ApaLI</u>	GTGCAC	GTGCM ⁶ AC	GTGCAM ⁵ C	Fo1,Ho1,Ho2
<u>ApyI</u>	CCWGG	C ^{m5} CWGG ^b	^{m5} CCWGG	Kl1,Mc11,Ra3
<u>AquI</u>	CYCGRG	?	^{m5} CYCGRG [#]	Ka7,Ka8
<u>AseI</u>	ATTAAT	ATT ^{m6} AAT	?	Ne1
<u>Asp700I</u>	GAAN ₄ TTC	GAm ⁶ AN ₄ TTC	G ^{m6} AAN ₄ TTC	Ne1
		GAAN ₄ TT ^{m5} C		
<u>Asp718I</u>	GGTACC	GGT ^{m6} A ^{m5} CC ^b	GGTAC ^{m5} C	Mu1,Ne4
			GGTA ^{m5} C ^{m5} C ^b	
<u>AsuII</u>	TTCGAA	TT ^{m5} CGAA	?	Ne1
<u>AtuCI</u>	TGATCA	?	TG ^{m6} ATCA	Ro3,Sc12
<u>AvaI</u>	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
<u>Ava</u> II	GGWCC	GGWC ^{m4} C ^b	GGW ^{m5} CC GGWC ^{m5} C GGW ^{hm5} C ^{hm5} C	Ba3,Ko3 Mc10,Mc11 Hu1
<u>Avi</u> II	AGCGCT	m ⁶ AGCGCT	AG ^{m5} CGCT	Ne1
<u>Bal</u> II	TGGCCA	?	TGG ^{m5} CCA# TGGC ^{m5} CA ^b	Gi1,Tr2
<u>Bam</u> HI	GGATCC	GGATC ^{m5} C GG ^{m6} ATCC GG ^{m6} ATC ^{m5} C GGATC ^{m4} C	GGAT ^{m4} CC# GGAT ^{m5} CC GGAT ^{hm5} C ^{hm5} C	Br8,Dr1,Ha1,Hu1 La7
<u>Bam</u> FI	GGATCC	GG ^{m6} ATCC	GGAT ^{m4} CC	An1,Sh1
<u>Bam</u> KI	GGATCC	GG ^{m6} ATCC	GGAT ^{m4} CC	An1,Sh1
<u>Ban</u> I	GGYRCC ^b	GG ^{m5} CGCC GGYRC ^{m4} C	?	Co3,Ka2
<u>Ban</u> II	GRGCYC	GRGCY ^{m5} C	GRG ^{m5} CYC	Fo1,Ne2,Ne6
<u>Ban</u> III	ATCGAT	?	ATCG ^{m6} AT	Su1
<u>Bbe</u> I	GGCGCC	GGCG ^{m5} CC GGCGC ^{m5} C	GG ^{m5} CGCC	Co3,Ne2,Sh2
<u>Bbi</u> II	GRCGYC	?	GR ^{m5} CGYC	Co3
<u>Bbr</u> PI	CACGTG	?	m ⁵ CAM ⁵ CGTG	Wo1
<u>Bbs</u> I	GAAGAC	GAAGAM ⁵ C	?	Fo1
<u>Bbv</u> I	GCWGC	?	G ^{m5} CWGC#	Do1,Ha1,Va5
<u>Bcl</u> II	TGATCA ^b	TGAT ^{m5} CA	TG ^{m6} ATCA TGAT ^{hm5} CA	Bi4,Br8,Eh3,Ro3 Hu1
<u>Bcn</u> I	CCSGG	m ⁵ CCSGG	C ^{m4} CSGG#	Ja3,Ja6,Kl1
<u>Bep</u> I	CGCG	?	m ⁵ CGCG	Ku2
<u>Bfr</u> I	CTTAAG	?	m ⁵ CTTAAG	Wo1
<u>Bgl</u> II	GCCN ₅ GGC	GC ^{m5} CN ₅ GGC ^b	G ^{m5} CCN ₅ GGC GCCN ₅ GG ^{m5} C ^b GC ^{m4} CN ₅ GGC ^b	Kl1,Ko3,Mc11,Ne2
<u>Bgl</u> III	AGATCT ^b	AG ^{m6} ATCT	AGAT ^{m5} CT AGAT ^{hm5} CT	Bi4,Br8,Dr1,Dy1,Eh3 Hu1,Pi6
<u>Bin</u> I	GGATC	?	GG ^{m6} ATC	Bo1
<u>Bma</u> DI	CGATCG	CG ^{m6} ATCG	CGAT ^{m6} CG	Qi2
<u>Bme</u> 216I	GGWCC	?	GGWC ^{m5} C	Ma9
<u>Bna</u> I	GGATCC	GG ^{m6} ATCC	GGAT ^{m4} CC GGAT ^{m5} CC#	Ne1
<u>Bsa</u> I	GGTCTC	?	GGTCT ^{m5} C	Fo1
<u>Bsa</u> AI	YACGTR	?	YA ^{m5} CGTR	Fo1
<u>Bsa</u> BI	GATN ₄ ATC	?	GATN ₄ AT ^{m5} C	Fo1
<u>Bsm</u> I	GAATGC	GAATG ^{m5} C	G ^{m6} AATGC	Fo1,Ne1
<u>Bsm</u> AI	GTCTC	?	GTCT ^{m5} C	Fo1
<u>Bsp</u> 106I	ATCGAT	?	ATCG ^{m5} AT#	Ne5

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
<u>Bsp</u> 1286I	GDGCHC	GDGCH ^{m5} C	GDG ^{m5} CHC	Fo1,Ne2,Ne6
<u>Bsp</u> HI	TCATGA	?	TC ^{m6} ATGA	Pa2
			TCATG ^{m6} A	Mc1
<u>Bsp</u> MI	ACCTGC	ACCTG ^{m5} C	?	Fo1
<u>Bsp</u> MII	TCCGGA	TCCGG ^{m6} A	T ^{m5} CCGGA	La2,Sc2
			TC ^{m5} CGGA	
<u>Bsp</u> NI	CCWGG	^{m5} CCWGG C ^{m5} CWGG	?	Ne4
<u>Bsp</u> XI	ATCGAT	?	ATCG ^{m6} AT	Zi1
<u>Bsp</u> XII	TGATCA	?	TG ^{m6} ATCA	Zi1
<u>Bss</u> HII	GCGCGC ^b	?	G ^{m5} CGCGC	Ne4,Qi3
<u>Bst</u> I	GGATCC	GG ^{m6} ATCC GGATC ^{m5} C	GGAT ^{m4} CC GGAT ^{m5} CC GGATC ^{m4} C	Ne4 Ne1
<u>Bst</u> BI	TTCGAA	?	TTCG ^{m6} AA TT ^{m5} CGAA	Ne4 Wo1
<u>Bst</u> EII	GGTNACC	GGTNA ^{m5} C ^{m5} C ^b GGTNAC ^{m4} C	GGTNA ^{hm5} C ^{hm5} C	Hu1,Mc11 Ne1
<u>Bst</u> EIII	GATC ^b	?	G ^{m6} ATC	My1,Ro3
<u>Bst</u> GI	TGATCA	?	TG ^{m6} ATCA	Ro3
<u>Bst</u> NI	CCWGG ^b	^{m5} CCWGG ^b C ^{m5} CWGG ^{m5} C ^{m5} CWGG ^b	^{hm5} C ^{hm5} CWGG C ^{m4} CWGG	Gr4,Hu1,Mc11,Ro3 Ne1
<u>Bst</u> UI	CGCG	?	^{m5} CGCG	Ne5
<u>Bst</u> XI	CCAN ₆ TGG	?	^{m5} CCAN ₆ TGG	Ne2
<u>Bst</u> YI	RGATCY	RG ^{m6} ATCY RGAT ^{m5} CY	RGAT ^{m4} CY	Ne4 Ne1
<u>Bsu</u> BI	CTGCAG	?	CTGC ^{m6} AG [#]	Ga1,Je1,St5,Sh1
<u>Bsu</u> EI	CGCG	?	^{m5} CGCG [#]	Ga1,Je1,St5,Sh1
<u>Bsu</u> FI	CCGG	?	^{m5} CCGG [#]	Je1
<u>Bsu</u> MI	CTCGAG	?	CT ^{m5} CGAG [#]	Je1
<u>Bsu</u> QI	CCGG	?	^m CCGG	Je2
<u>Bsu</u> RI	GGCC	?	GG ^{m5} CC [#] ^b	Gu6,Ki2,Ki3
<u>Ccr</u> I	CTCGAG	?	CTCG ^{m6} AG	Ne1
<u>Cfo</u> I	GCGC	?	G ^{m5} CGC G ^{hm5} C ^{Ghm5} C	Eh1 Hu1
<u>Cfr</u> I	YGGCCR	?	YGG ^{m5} CCR [#]	Kl1
<u>Cfr</u> 6I	CAGCTG	?	CAG ^{m4} CTG [#] CAG ^{m5} CTG	Bu5 Bu6
<u>Cfr</u> 9I	CCCGGG ^b	C ^{m5} CCCGG CC ^{m5} CGGG	^{m4} CCCGGG ^{m5} CCCGGG C ^{m4} CCCGG [#] CC ^{m4} CGGG	

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
<u>Cfr</u> 10I	RCCGGY	?	Rm ⁵ CCGGY#	Bi5,Kl1
<u>Cfr</u> 13I	GGNCC	?	GGNm ⁵ CC#	Bi5,Kl1
<u>Cla</u> I	ATCGAT	?	m ⁶ ATCGAT	Ca4,Mc11,Mc12,Ne4
			ATm ⁵ CGAT	Wo1
			ATCGm ⁶ AT#	Mc3
<u>Cpe</u> I	TGATCA	?	TGm ⁶ ATCA	Fi1,Ro3
<u>Csp</u> I	CGGWCCG	CGGWcm ⁵ CG	CGGWm ⁵ CCG	Mc11
			m ⁵ CGGWCCG	
<u>Csp</u> 45I	TTCGAA	?	TTCGm ⁶ AA	Ne4,Sc11
<u>Cty</u> I	GATC	?	Gm ⁶ ATC#	Ri2
<u>Cvi</u> AI	GATC	?	Gm ⁶ ATC	Xi1,Xi6
<u>Cvi</u> BI	GANTC	?	Gm ⁶ ANTC#	Xi3
<u>Cvi</u> JI	RGCY	?	RGm ⁵ CY#	Sh3,Xi2
<u>Cvi</u> PI	CC	Cm ⁵ C	m ⁵ CC#	Xi4
<u>Cvi</u> QI	GTAC	GTA ^{m5} C	GTm ⁶ AC#	Xi2,Xi5
<u>Dde</u> I	CTNAG	?	m ⁵ CTNAG#	Ho3,Ne2
			hm ⁵ CTNAG	Hu1
<u>Dpn</u> I	Gm ⁶ ATC ^b	Gm ⁶ ATC	GATC	La3,Mc11,Vo1
		Gm ⁶ ATm ⁵ C ^b	GATm ⁴ C	Ne4
		Gm ⁶ ATm ⁴ C	GATm ⁵ C	Ne5
<u>Dpn</u> II	GATC	?	Gm ⁶ ATC#	De1,La3,La4,La5,Ma6,Vo1
<u>Dra</u> I	TTTAAA	TTTA ⁶ AA	?	Ne1
<u>Dra</u> II	RGGNCCY	?	RGGNcm ⁵ CY	Sc8
<u>Eae</u> I	YGGCCR	?	YGGm ⁵ CCR#	Ja2,Wh1
			YGGcm ⁵ CR	
<u>Eag</u> I	CGGCCG	?	CGGm ⁵ CCG	Mc11
			m ⁵ CGGcm ⁵ CG	
<u>Ear</u> I	GAAGAG	?	Gm ⁶ AAGAG	Ne4
			GAAGm ⁶ AG	
			m ⁵ CTm ⁵ CTTm ⁵ C	Ne1
<u>Eca</u> I	GGTANm ⁶ ACC	?	GGTAm ⁶ ACC#	Br2
<u>Ecl</u> XI	CGGCCG	?	m ⁵ CGGcm ⁵ CG	Qi3
			CGGm ⁵ CCG	
<u>Eco</u> 47I	GGWCC	?	GGWcm ⁵ C	Ja5
<u>Eco</u> 47III	AGCGCT	m ⁶ AGCGCT	AGm ⁵ CGCT	Ne1,Ne4
<u>Eco</u> A	GAGN ₇ GTCA ^b	?	Gm ⁶ AGN ₇ GmTCA# ^b	Bi2,Co6,Fu2
<u>Eco</u> B	TGAN ₈ TGCT ^b	?	TGm ⁶ AN ₈ mTGCT# ^b	Bi2,La10,La11
<u>Eco</u> DXXI	TCAN ₇ AATC ^b	?	TCAN ₇ m ⁶ AAmTC# ^b	Pi1
<u>Eco</u> E	GAGN ₇ ATGC	?	Gm ⁶ AGN ₇ ATGC	Co6,Fu2
<u>Eco</u> K	AACN ₆ GTGC ^b	?	Am ⁶ ACN ₆ GmTGC# ^b	Bi2,Bi3,Ka1
<u>Eco</u> O109I	RGGNCCY	?	RGGNcm ⁵ CY	Sc8
<u>Eco</u> PI	AGACC ^b	AGA ^{hm5} C ^{hm5} C	AGm ⁶ ACC#	Ba1,Ba2,Ha2,Re4
<u>Eco</u> P15	CAGCAG ^b	?	Cm ⁶ AGCAG#	Hu2

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
<u>EcoRI</u>	GAATTC	GAATT ^{hm5} C	G ^{m6} AATTC ^b GA ^{m6} ATTC [#] GAATT ^{m5} C ^b	Mc11,Ne2,Ru1 Br1,Br8,Du1 Hu1,Ka3,Ta1
<u>EcoRII</u>	CCWGG	m ⁵ CCWGG ^b	m ⁴ CCWGG C ^{m4} WGG C ^{m5} WGG [#] CC ^{m6} AGG hm ⁵ Chm ⁵ WGG	Ku3,Yo1 Bu4,Na5,Ro3 Bo5,Mc11 Bu3 Hu1,Ka3
<u>EcoRV</u>	GATATC	GATAT ^{m5} C ^b	G ^{m6} ATATC [#] GAT ^{m6} ATC	Mc11,Ne2,Wo1 Fl1
<u>EcoR124</u>	GAAN ₆ RTCG ^b	?	GA ^{m6} AN ₆ RTCG GAAN ₆ R ^m TCG	Pr2,Pr3 Bi1
<u>EcoR124/3</u>	GAAN ₇ RTCG ^b	?	m ⁶ A	Pr1,Pr2
<u>EheI</u>	GGCGCC	?	GGCGCC	Co2
<u>EspI</u>	GCTNAGC	GCTNAG ^{m5} C	G ^{m5} CTNAGC	Ne4
<u>Fnu4HI</u>	GCNGC	?	G ^{m5} CNGC GCNG ^{m5} C	Ko3,Tr2
<u>FnuDII</u>	CGCG	?	m ⁵ CGCG CG ^{m5} CG	Ga1,Ga2,Ne2,Ne6,St6
<u>FnuEI</u>	GATC	G ^{m6} ATC ^b	?	Lu1,Ne2
<u>FokI</u>	CATCC	CAT ^{m5} CC CATC ^{m5} C ^b CATC ^{m4} C	GG ^{m6} ATG C ^{m6} ATCC	Po3,Po4,Sc2 Ne1
<u>FseI</u>	GGCCGGCC	?	GG ^{m5} CCGG ^{m5} CC GGC ^{m5} CGGCC GG ^{m5} CCGGCC	Ne7
<u>FspI</u>	TGCGCA	?	TG ^{m5} CGCA	Ne4
<u>HaeII</u>	RGCGCY ^b	?	RG ^{m5} CGCY RG ^{hm5} CG ^{hm5} CY	Eh2,Gr4,Ka2,Ko3,Mc11,Pi5 Hu1
<u>HaeIII</u>	GGCC	GGC ^{m5} C	GG ^{m5} CC ^{#b} GG ^{hm5} Chm ⁵ C	Ba3,Ka2,Ko3,Ma5 Hu1
<u>HapII</u>	CCGG	?	C ^{m5} CGG [#]	Eh2,Wa1
<u>HgaI</u>	GACGC	?	GA ^{m5} CGC GACG ^{m5} C	Ne1 Mc11
<u>HgiAI</u>	GRGCYC	GRGCY ^{m5} C	GRG ^{m5} CYC	Fo1,Ne2,Wh3
<u>HgiCI</u>	GGYRCC	?	GGYRC ^{m5} C	Er1
<u>HgiCII</u>	GGWCC	?	GGWC ^{m5} C	Er1
<u>HgiEI</u>	GGWCC	?	GGWC ^{m5} C	Er1
<u>HgiJII</u>	GGYRCC	?	GGYRC ^{m5} C	Wh3
<u>HhaI</u>	GCGC	?	G ^{m5} CGC [#] GCG ^{m5} C G ^{hm5} CG ^{hm5} C	Eh2,Ko3,Sm1 Mc11, Hu1

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
<u>Hha</u> II	GANTC	?	Gm ⁶ ANTC [#]	Ma5
<u>Hinc</u> II	GTyrAC	GTyRAM ⁵ C	GTyRm ⁶ AC GTyRA ^{hm5} C	Gr4,Ro7 Hu1
<u>Hind</u> II	GTyrAC	?	GTyRm ⁶ AC [#]	Ro7
<u>Hinf</u> I	GANTC	GANTm ⁵ C ^b	Gm ⁶ ANTC GANT ^{hm5} C	Ch1,Co1,Ne2,Pe1 Hu1
<u>Hind</u> III	AAGCTT	?	m ⁶ AAGCTT [#] AAGm ⁵ CTT AAG ^{hm5} CTT	Br8,Gr4,Ro7 Ne2 Hu1,Ka3
<u>Hin</u> PI	GCGC	?	Gm ⁵ CGC	Mc11,Ne6
<u>Hpa</u> I	GTTAAC	GTTAAM ⁵ C	GTTA ^{m6} AC [#] GTTA ^{hm5} C	Br8,Gr4,Hu1,Yo3 Hu1
<u>Hpa</u> II	CCGG	?	m ⁴ CCGG m ⁵ CCGG ^b Cm ⁴ CCGG ^b Cm ⁵ CCGG [#] hm ⁵ C ^{hm5} CCGG	Be3,Bu6,Eh2,Ma5 Ko3,Qu1,Wa5 Hu1
<u>Hph</u> I	TCACC	TCACm ⁵ C	Tm ⁵ CACC [#] GGTGm ⁶ A	Fo1,Mc11,Ne2
<u>Kpn</u> I	GGTACC ^b	GGTAm ⁵ CC GGTACm ⁵ C GGTAm ⁵ Cm ⁵ C ^b	GGTm ⁶ Am ⁵ CC GGTACm ⁴ C	Eh3,Mc11,Ne2 Ne1
<u>Kpn</u> 2I	TCCGGA	TCCGGm ⁶ A	Tm ⁵ CCGGA TCm ⁵ CGGA	Mc1,Ne1 Ne1
<u>Ksp</u> I	CCGCGG	?	m ⁵ CCGCGG Cm ⁵ CCGCGG	Ne1 Qi2
<u>Mae</u> II	ACGT	?	Am ⁵ CGT ^b	Mo2
<u>Mam</u> I	GATN ₄ ATC	?	Gm ⁶ ATN ₄ m ⁶ ATC	St4
<u>Mbo</u> I	GATC ^b	GATm ⁴ C GATm ⁵ C ^b	Gm ⁶ ATC [#] GAT ^{hm5} C	Br5,Ge1,Mc8 Hu1,Ro3
<u>Mbo</u> II	GAAGA	Tm ⁵ CTTm ⁵ C ^b Gm ⁶ AAGA	GAAGm ⁶ A [#]	Ba3,Mc11,Mc12,Ne2
<u>Mfi</u> II	RGATCY ^b	?	RGm ⁶ ATCY RGATm ⁴ CY RGATm ⁵ CY	On1
<u>Mlu</u> I	ACGCGT	m ⁶ ACGCGT	Am ⁵ CGCGT	Mc11,Sh1,St5,Qi3
<u>Mlu</u> 9273I	TCGCGA	?	Tm ⁵ CGCGA	Ne1
<u>Mlu</u> 9273II	GCCGGC		Gm ⁵ CCGGC GCm ⁵ CCGGC	Ne1
<u>Mme</u> II	GATC	?	Gm ⁶ ATC	Bo4
<u>Mnl</u> II	CCTC ^b	?	m ⁵ CCTC m ⁵ Cm ⁵ CTm ⁵ C	Eh3,Mc11

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
<u>Mph</u> I	CCWGG ^b	?	Cm ⁵ CWGG	Ro3
<u>Mro</u> I	TCCGGA	TCCGGm ⁶ A	Tm ⁵ CCGGA	Mc1,Ne1
			TCm ⁵ CGGA	Ne1
<u>Mse</u> I	TTAA	TTm ⁶ AA	?	Ne1
<u>Msp</u> I	CCGG ^b	m ⁴ CCGG	m ⁵ CCGG#	Eh2,Je2,Va3,Wa1,Wa5
		Cm ⁴ CGG	hm ⁵ C ^h m ⁵ CGG	Bu6,Hu1
		Cm ⁵ CGG		
<u>Mst</u> II	CCTNAGG	m ⁵ CCTNAGG	?	Mc11
<u>Mva</u> I	CCWGG	Cm ⁵ CWGG ^b	Cm ⁴ CWGG#	Bu4,Ku1
		m ⁵ CCWGG	CCm ⁶ AGG ^b	Gr3,Ku3
			m ⁴ CCWGG ^b	
			m ⁵ Cm ⁵ CWGG ^b	Ne1
<u>Mvn</u> I	CGCG	?	m ⁵ CGCG	Ne1
<u>Nae</u> I	GCCGGC ^b	?	Gm ⁵ CCGGC	Eh3,Kl1,Mc11,Ne5
			GCm ⁵ CGGC	
			GCCGGm ⁵ C	
<u>Nan</u> II	Gm ⁶ ATC ^b	Gm ⁶ ATC	GATC	Pa1,Ne5
		Gm ⁶ ATm ⁵ C ^b	GATm ⁵ C	
<u>Nar</u> I	GGCGCC	GGCGCm ⁵ C	GGm ⁵ CGCC	Ko3,Mc11,Ne5
			GGCGCm ⁴ C	Ne1
<u>Nci</u> I	CCSGG	m ⁵ CCSGG	Cm ⁴ CSGG	Br8,Ko3,Mc11
			Cm ⁵ CSGG ^b	
<u>Nco</u> I	CCATGG	CCm ⁶ ATGG	m ⁴ CCATGG ^b	Kl1,Ne2,Ne4
			m ⁵ CCATGG	
<u>Ncr</u> I	AGATCT	AGm ⁶ ATCT ^b	?	Qi1
<u>Ncu</u> I	GAAGA	GAAGm ⁶ A	?	Mc13
<u>Nde</u> I	CATATG	m ⁵ CATATG ^b	m ⁶ A	Be4,Mc11
<u>Nde</u> II	GATC	GATm ⁵ C ^b	Gm ⁶ ATC	Mc9
<u>Ngo</u> BI	TCACC	?	Tm ⁵ CACC	Pi3,Pi4
<u>Ngo</u> PI	RGCGCY	?	RGm ⁵ CGCY	Ko3,Ko5
<u>Ngo</u> PII	GGCC	?	GGm ⁵ CC#	Ko3,Ko5
			GGCm ⁵ C ^b	Su3,Su4
<u>Nhe</u> I	GCTAGC	?	GCTAGm ⁵ C	Kl1,Mc11,Ne2
<u>Nla</u> III	CATG	?	Cm ⁶ ATG#	La1,Mo3
<u>Nmu</u> DI	Gm ⁶ ATC ^b	Gm ⁶ ATC	GATC	Pa1
<u>Nmu</u> EI	Gm ⁶ ATC ^b	Gm ⁶ ATC	GATC	Pa1
<u>Not</u> I	GCGGCCGC	GCGGCCGm ⁵ C	GCGGm ⁵ CCGC	Mc11
			GCGGm ⁵ CGC	St5,Qi2
<u>Nru</u> I	TCGCGA	TCGm ⁵ CGA	Tm ⁵ CGCGA	Ne1,Qi3
			TCGCGm ⁶ A	Ne2
<u>Nsi</u> I	ATGCAT	?	ATGm ⁶ AT	Be5
			ATGm ⁵ CAT	Wo1

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
<u>NspBII</u>	CMGCKG	Cm ⁵ CGCKG	?	Ne1
<u>PfiMI</u>	CCAN ₅ TGG	?	Cm ⁴ CAN ₅ TGG	Ne1
			Cm ⁵ CAN ₅ TGG	St7
<u>PfaI</u>	GATC	Gm ⁶ ATC	?	Ro3
<u>PfuI</u>	CGTACG	?	CGTAm ⁵ CG	Ne1
<u>PaeR7I</u>	CTCGAG	?	CTCGm ⁶ AG [#]	Gi3
			CTm ⁵ CGAG	Gh1
<u>PmlI</u>	CACGTG	?	CAM ⁵ CGTG	Fo1
<u>PpuAI</u>	CGTACG	?	CGTAm ⁵ CG	Ne1
<u>PstI</u>	CTGCAG	?	m ⁵ CTGCAG	Do1,Gr4,Mc11,Ne2
			CTGcm ⁶ AG [#]	
<u>PvuI</u>	CGATCG ^b	CGm ⁶ ATCG	CGATm ⁴ CG	Br8,Bu3,Eh3
			CGATm ⁵ CG	
<u>PvuII</u>	CAGCTG	?	CAGm ⁴ CTG [#]	Br8,Bu5,Do1
			CAGm ⁵ CTG	Eh3,Ja3,Ro1
<u>Rrh4273I</u>	GTCGAC	?	GTCGm ⁶ AC	Ba6
<u>RsaI</u>	GTAC ^b	GTAm ⁵ C ^b	Gtm ⁶ Am ⁵ C	Eh3,Ne4,Ne5
<u>RshI</u>	CGATCG	CGm ⁶ ATCG	?	Ly1
<u>RspXI</u>	TCATGA	?	TCm ⁶ ATGA	Pa2
			TCATGm ⁶ A	Ne4
<u>RsrI</u>	GAATTC	?	Gm ⁶ AATTC	Mc11
			GAm ⁶ ATTC ^{#b}	Ba5
<u>RsrII</u>	CGGWCCG	?	m ⁵ CGGWCCG	Mc11,Qi3
			CGGWm ⁵ CCG	
			CGGWcm ⁵ CG	
<u>SacI</u>	GAGCTC	Gm ⁶ AGCTC	GAGm ⁵ CTC	Mc11
<u>SacII</u>	CCGCGG	?	m ⁵ CCGCGG	Kl1,Ne2
<u>SalI</u>	GTCGAC	GTCGAm ⁵ C	Gtm ⁵ CGAC	Br8,Eh2,Lu2,Qi1
			GTCGm ⁶ AC [#]	Mc3,Ro4,Ro5,Va4
<u>SalDI</u>	TCGCGA	TCGCGm ⁶ A	Tm ⁵ CGCGA	Mc13,Ne1,Qi3
<u>Sau3AI</u>	GATC ^b	Gm ⁶ ATC	GATm ⁵ C ^{#b}	Dr1,Eh2,Ja3,Mc3,Ro3,Se1
			GATm ⁴ C	Ne5
			GAThm ⁵ C	Hu1
<u>Sau96I</u>	GGNCC	?	GGNm ⁵ CC [#]	Ko3,Ne2,Pe1
			GGNCm ⁵ C	
			GGNhm ⁵ Chm ⁵ C	Hu1
<u>Sbo13I</u>	TCGCGA	TCGCGm ⁶ A	Tm ⁵ CGCGA	Mc11,Ne1
<u>ScaI</u>	AGTACT	AGTAm ⁵ CT	?	Wo1
<u>ScrFI</u>	CCNGG	m ⁵ CCNGG	Cm ⁵ CNNG	Mc11,Ne2
			Cm ⁴ CNNG	Ne1
<u>SfaNI</u>	GATGC	GATGm ⁵ C	Gm ⁶ ATGC	Mc11,Po4
<u>SfiI</u>	GGCCN ₅ GGCC	GGm ⁵ CCN ₅ GGm ⁵ CC ^b	GGcm ⁵ CN ₅ GGCC	Mc11,Qi2
		GGCCN ₅ GGcm ⁵ C		
<u>SfiII</u>	CTGCAG	?	CTGcm ⁶ AG	Br8

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
<u>Sgr</u> AI	CRCCGGYG	?	CRCm ⁵ CGGYG	Ta3
<u>Sin</u> I	GGWCC	?	GGWm ⁵ CC#	Ka5,Ka6
<u>Sma</u> I	CCCGGG	Cm ⁵ CCGGG	m ⁴ CCCGGG	Br8,Bu6,Eh2,Ga4
			m ⁵ CCCGGG ^b	Ja3,Ka7,Mc3,Qu1
			Cm ⁴ CCGGG ^b	
			CCm ⁴ CGGG	
			CCm ⁵ CGGG ^b	
<u>Sna</u> BI	TACGTA	?	TAm ⁵ CGTA	Fo1
<u>Sno</u> I	GTGCAC	?	GTGm ⁵ CAm ⁵ C	Ho2,Wo1
<u>Spe</u> I	ACTAGT	?	m ⁶ ACTAGT	Ho1
			Am ⁵ CTAGT	Wo1
<u>Sph</u> I	GCATGC	GCATGm ⁵ C Ghm ⁵ CATGhm ⁵ C	GCm ⁶ ATGC	Mc11,Ne2,Mo3
<u>Spl</u> II	CGTACG	CGTm ⁶ ACG	?	Ne4,Qi3
<u>Spo</u> I	TCGCGA	TCGCGm ⁶ A	Tm ⁵ CGCGA	Ne1,Ne4
			TCGm ⁵ CGA	
<u>Sso</u> II	CCNGG	?	Cm ⁵ CNGG	Vi1
			m ⁵ CCNGG	Gr3
<u>Sso</u> 47I	GAATTC	?	Gm ⁶ AATTC#	Ni4
<u>Ssp</u> I	AATATT	m ⁶ AATATT	?	Ne1
<u>Sst</u> I	GAGCTC	?	GAGm ⁵ CTC	Br8,Ro1
			GAGhm ⁵ CThm ⁵ C	Hu1
<u>Stu</u> I	AGGCCT	?	AGGm ⁵ CCT	Ca4,Mc11
			AGGCm ⁵ CT	So3
			AGGCm ⁴ CT	Ne1
<u>Sty</u> SBI	GAGN ₆ RTAYG ^b	?	Gm ⁶ AGN ₆ Rm ⁵ TAYG# ^b	Na1,Na2
<u>Sty</u> SPI	AACN ₆ GTRC ^b	?	Am ⁶ ACN ₆ Gm ⁵ TRC# ^b	Na1,Na2
<u>Taq</u> I	TCGA	Tm ⁵ CGA ^b Thm ⁵ CGA ^b	TCGm ⁶ A#	Gr4,Hu1,Mc3,Va3
<u>Taq</u> II	GACCGA CACCCA	?	Gm ⁶ ACCGA	Hu1 Ne4
<u>Taq</u> XI	CCWGG	m ⁵ CCWGG Cm ⁵ CWGG	?	Gr1
<u>Tfi</u> I	GAWTC	GAWTm ⁵ C	?	Fo1
<u>Tfi</u> II	TCGA	?	TCGm ⁶ A	Sa3,Va6
<u>Tha</u> I	CGCG	m ⁵ CGCG	m ⁵ CGCG	Ga1,Ne1
			hm ⁵ CGhm ⁵ CG	Hu1
<u>Tth</u> HBI	TCGA	Tm ⁵ CGA	TCGm ⁶ A#	Sa3
<u>Xba</u> I	TCTAGA	?	TCTAGm ⁶ A#	Mc13,We1
			Tm ⁵ CTAGA	Gr4,Hu1,Ne2
			Thm ⁵ CTAGA	

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
<u>XhoI</u>	CTCGAG ^b	?	CT ^{m5} CGAG CTCG ^{m6} AG m ⁵ CTCGAG	Br8,Eh2,Eh3,Ka7 Mc3,Va3
<u>XhoII</u> <u>XmaI</u>	RGATCY CCCGGG	RG ^{m6} ATCY CC ^{m5} CGGG ^b	RGAT ^{m5} CY ^b m ⁴ CCCGGG m ⁵ CCCGGG C ^{m4} CCGGG CC ^{m4} CGGG	Br8 Bu6,Yo5,Yo6
<u>XmaIII</u> <u>XmnI</u>	CGGCCG GAAN ₄ TTC	? GA ^{m6} AN ₄ TTC	CGG ^{m5} CCG G ^{m6} AAN ₄ TTC GAAN ₄ TT ^{m5} C ^b	Ne2,Tr2 Mc11,Ne2
<u>XorII</u>	CGATCG	CG ^{m6} ATCG	CGAT ^{m5} CG hm ⁵ CGAT ^{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; ^mC = methylcytosine, N4 or C5-methylcytosine unspecified; ^{m6}A = N6-methyladenine. Nomenclature is according to (Sm2) and (Co4).

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

AflI cuts slowly at GGWC^{m4}C.

AhaII (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).

Asp718I cuts M⁻CviQI-modified (GT^{m6}AC) *Chlorella* virus NY2A DNA. *Asp718I* does not cut GGTAC^{m5}CWGG overlapping *dcm* sites (Mu1) or ^{m5}C-substituted phage XP12 DNA, whereas *KpnI* cuts XP12 readily (Ne4).

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

AvaII 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).

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

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

BglI cleavage rate at certain GC^{m5}CN₅GGC, GC^{m4}CN₅GGC, and GCCN₅GG^{m5}C hemi-methylated sites is extremely slow. However, ^{m5}C bi-methylated M⁻HaeIII–*BglI* sites are completely refractory to *BglI* (Ko3,Ne2).

BssHII does not cut M⁻HhaI-modified DNA, in which two different cytosine positions are hemi-methylated, G^{m5}CGCGC/GCG^{m5}CGC (Ne4).

M⁻*BstI* modifies the internal cytosine GGAT^mCC, but it is not known whether this modification is ^{m5}C or ^{m4}C (Le2).

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

BstNI cuts C^{m5}CWGG, ^{m5}CCWGG and ^{m5}C^{m5}CWGG (Ne5). *BstNI* isoschizomers that are insensitive to C^{m5}CWGG include *AorI*, *ApyI*, *BspNI*, *MvaI* and *TaqXI* (Mc4).

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

Cfr9I, see reference Bu6 for rate effects.

M⁻*CreI* is from the unicellular eukaryote *Chlamydomonas reinhardtii* (Sa2).

DpnI requires adenine methylation on both DNA strands. Isoschizomers of *DpnI* include *CfuI*, *NanII*, *NmuEI*, *NmuDI* and *NsuDI* (Ca1). *DpnI* 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.

EcoA, *EcoB*, *EcoD*, *EcoDXXI*, *EcoK* are Type I restriction endonucleases. ^mT represents a 6-methyladenine in the complementary strand.

EcoPI is a Type III restriction endonuclease (Ba2,Ba1,Ha2).

EcoP15 is a Type III restriction endonuclease (Hu2).

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* (Ne5). *EcoRI* 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).

EcoRII isoschizomers that are sensitive to C^{m5}CWGG include *AtuBI*, *AtuII*, *BstGII*, *BinSI*, *Cfr5I*, *CfrII I*, *EclII*, *EcalI*, *Eco27I*, *Eco38I* and *MphI* (Ro3). *EcoRII* shows reduced rate of cleavage at hemi-methylated ^{m5}CCWGG/CCWGG sites (Yo1).

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

EcoR124 and *EcoR124/3* are Type I restriction endonucleases. ^mT represents a 6-methyladenine in the complementary strand. *EcoR124* is a Type I restriction endonuclease.

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

M⁻*FokI* in ref Po3 corresponds to M⁻*FokIA* in ref Po4.

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

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

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

HpaII 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 *HpaII* rate effects.

KpnI sensitivity to hemi-methylated GGTA^{m5}CC and GGTAC^{m5}C sites has been reported. *KpnI* 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).

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

MboI isoschizomers that are sensitive to G^{m6}ATC include *BssGII*, *BsaPI*, *Bsp74I*, *Bsp76I*, *Bsp105I*, *BstXII*, *BstEIII*, *BssGII*, *CpaI*, *CryI*, *CviAI*, *CviBII*, *CviHI*, *DpnII*, *FnuAII*, *FnuCI*, *HaeI*, *MeuI*, *MkrAI*, *MmeII*, *MnoIII*, *MosI*, *Msp67II*, *MthI*, *MthAI*, *NdeII*, *NfiAII*, *NfiBI*, *NfiI*, *NlaDI*, *NlaII*, *NmeCI*, *NphI*, *NsiAI*, *NspAI*, *NsuI*, *Pfal*, *RluI*, *SalAI*, *SalHI*, *Sau6782I*, *SinMI*, *TruII* (Ro3).

MboII 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).

MflI cuts slowly at ^{m6}AGATCY sites (On1).

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

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

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

NanII requires adenine methylation on both DNA strands (Ca1). *NanII* cuts M-*Eco dam* modified XP12 DNA (Ne5).

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

NcoI is blocked by M-*SecI* (CCNNGG) (Ne5).

NcrI is a *BglII* isoschizomer from *Nocardia carnia* Beijing (Qi1).

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

NdeII 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*.

NgoPII does not cut overlapping dcm sites (Su4).

NmuDI requires adenine methylation on both DNA strands (Ca1).

NmuEI requires adenine methylation on both DNA strands (Ca1).

PaeRI 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).

RsaI 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 *Asp718I*, but not by *RsaI* or *KpnI* (Ne4). It is likely that M-*RsaI* specifies GTA^{m4}C; and high levels of ^{m4}C are present in *R. sphaeroides* DNA (Eh3).

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 (St3). *Sau3AI* cuts at a reduced rate at ^{m6}AGATC (On1). *Sau3AI* isoschizomers that are insensitive to G^{m6}ATC include *Bce243I*, *Bsp49I*, *Bsp51I*, *Bsp52I*, *Bsp54I*, *Bsp57I*, *Bsp58I*, *Bsp59I*, *Bsp60I*, *Bsp61I*, *Bsp64I*, *Bsp65I*, *Bsp66I*, *Bsp67I*, *Bsp72I*, *BspAI*, *Bsp91I*, *BsrPII*, *CpfI*, *Csp5I*, *CpeI*, *FnuEI*, *MspBI*, *SauCI*, *SauDI*, *SauEI*, *SauFI*, *SauGI* and *SauMI* (Ro3).

SfiI cannot cut M-*BglI*-modified DNA (Ne1).

SmaI nicking occurs in the unmethylated strand of the hemi-methylated sequence CC^{m5}CGGG/CCCGGG (Bu6,Wa5). *SmaI* 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 *SmaI*: ^{m5}CCCCGGG is not cut when modified by M-*AquI* methyltransferase (Ka7) or at overlapping M-*HaeIII-SmaI* sites (GG^{m5}CCCCGGG, Ne5). Other investigators have reported that *SmaI* cuts at a reduced rate at hemi-methylated ^{m5}CCCCGGG sites (Bu6).

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

SrySBI and *SrySPI* are Type I restriction endonucleases. ^{mT} represents a 6-methyladenine in the complementary strand.

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

M-*TaqI* methylates T^{m5}CGA at least 20 fold slower than unmodified TCGA (Mc7).

XbaI will cut T^{m5}CTAGA/TCTAGA hemi-methylated DNA at high enzyme levels (>100U *XbaI*/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 (Br8). See reference Bu6 for rate effects.

XmnI cuts the fully ^{m5}C substituted phage XP12 DNA (Ne5). *XmnI* cuts slowly at some sites in DNA methylated on both strands at GAAN₄TT^{m5}C (Ne5).

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

<u>Methylase</u> ^a	<u>Specificity</u> ^a	<u>References</u>
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 and G ^{m6} AGAC	Bu4 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 and G ^{m5} CNGC	Be1,Gu5,Gu4,No2,No3 No1,Tr1

<u>Methylase</u> ^a	<u>Specificity</u> ^a	<u>References</u>
M· <u>Bsup</u> 11I	GGm ⁵ CC and Gm ⁵ CNGC	Gu4,Gu5,Gu7,No1,No2
M· <u>Bsup</u> 11s	GGCC and GDGCHC	Be1
M· <u>Bsu</u> QI	mCCGG	Je2
M· <u>Bsu</u> RI	GGm ⁵ CC ^b	Gu6,Ki2,Ki3
M· <u>Bsu</u> SPβ	GGm ⁵ CC and Gm ⁵ CNGC	Gu4,Gu5,Gu7,Je2,Ki2,N16
M· <u>Bsu</u> SPRI	GGm ⁵ CC and m ⁵ Cm ⁵ CGG and Cm ⁵ CWGG	No2,Tr1,Tr3 Be1,Gu5,Gu7,No2 Po1
M· <u>Bsu</u> SPR191	m ⁵ Cm ⁵ CGG and Cm ⁵ CWGG	Be2,Bu1,Gu3,Gu5,Ki2,Po1 Je2,No2,Po1
M· <u>Bsu</u> SPR83I	GGm ⁵ CC and Cm ⁵ CWGG	Gu3
M· <u>Cfr</u> A	GCA ₈ GTGG	Da2,Da3
M· <u>Cfr</u> I	YGGm ⁵ CCR	Po6
M· <u>Cfr</u> 6I	CAGm ⁴ CTG	Bu5
M· <u>Cfr</u> 9I	Cm ⁴ CCGGG	Kl3,Po6
M· <u>Cfr</u> 10I	Rm ⁵ CCGGY	Po6
M· <u>Cfr</u> 13I	GGNm ⁵ CC	Bi5
M· <u>Cla</u> I	ATCGm ⁶ AT	Mc3
M· <u>Cre</u> I	Tm ⁵ CR	Sa2 (Chlamydomonas)
M· <u>Cty</u> I	Gm ⁶ ATC#	Ri2
M· <u>Cvi</u> BI	Gm ⁶ ANTC	X2
M· <u>Cvi</u> BIII	TCGm ⁶ A	Na4
M· <u>Cvi</u> JI	RGm ⁵ CY	Sh3
M· <u>Cvi</u> PI	m ⁵ CC	Xi4
M· <u>Cvi</u> QI	GTm ⁶ AC	Xi2,Xi5
M· <u>Cvi</u> RI	TGm ⁶ A	St1
M· <u>Cvi</u> RII	GTm ⁶ AC	St1
M· <u>Dde</u> I	m ⁵ CTNAG	Ho3,Lu2,Sz3
M· <u>Dpn</u> II	Gm ⁶ ATC	De1,La3,La4,La5,Ma6
M· <u>Dpn</u> A	?Gm ⁶ ATC?	De1
M· <u>Eae</u> I	YGGm ⁵ CCR	Ja1,Wh1
M· <u>Eag</u> I	CGGCCG	Sz2
M· <u>Eca</u> I	GGTm ⁶ ACC	Br2
M· <u>Eco</u> dam	Gm ⁶ ATC	Br6,Bu9,Dr1,Gi2,Ha2,He2,Ur1
M· <u>Eco</u> dcmI	Cm ⁵ CWGG	Bo5,Ma10,So2,Ur1
M· <u>Eco</u> dcmII	Rm ⁵ CCGG	Bu8,Ne8
M· <u>Eco</u> dcmIII	mCCWGG	Ni2
M· <u>Eco</u> dcmIV	GGWCm ⁵ C	Mo1,Ni2
M· <u>Eco</u> A	Gm ⁶ AGN ₇ Gm ⁵ TCA ^b	Co7,Fu2
M· <u>Eco</u> B	TGm ⁶ AN ₈ Gm ⁵ TGCT ^b	Go3
M· <u>Eco</u> D	TTAN ₇ GTCY ^b	Go3

<u>Methylase</u> ^a	<u>Specificity</u> ^a	<u>References</u>
M·EcoDXXI	TCAN ₇ ATTC ^b	Sk1
M·EcoE	GAGN ₇ ATGC ^b	Fu2
M·EcoK	Am ⁶ ACN ₆ G ^m TGC ^b	Bo2,Go3,Ka1,Lo2,Sa1
M·EcoPI	AG ^{m6} ACC ^b	Ba2,Hu2
M·Eco P1 dam	Gm ⁶ ATC ^b	Co5
M·EcoP15	Cm ⁶ AGCAG	Hu2
M·EcoRI	GA ^{m6} ATTC	Du1,Gr2,Ke2
		Ne2,Ne9,Ru1
M·EcoRII	Cm ⁵ CWGG	Bh1,Bu7,Bu8,Ko6,Ko7,Ko8
		Ma10,Sc6,So1,Yo4
M·EcoRV	Gm ⁶ ATATC	Bo3
M·EcoR124	GAAN ₆ RTCG (m ⁶ A)	Pr2,Pr3
M·EcoR124/3	GAAN ₇ RTCG (m ⁶ A)	Pr2,Pr3
M·EcoT1 dam	Gm ⁶ ATC	Sc1,Sc7
M·EcoT2 dam	Gm ⁶ AT	Br7,Ha2,Ha3,Mi1,Sc4,Sc5
M·EcoT4 dam	Gm ⁶ ATC	Ha4,Ma1,Mi2,Sc3,Sc4,Sc5
M·Eco31I	GGT ^{m5} CTC	Bu4
	and Gm ⁶ AGACC	Bu4
M·Eco47II	GGNCC	Po6
M·Eco51I	CTGAAG (m ⁶ A)	Po6
M·Eco57I	CTGAAG (m ⁶ A)	Po6
M·Eco64I	GGYRCC	Po6
M·Eco72I	CACGTG (m ⁵ C)	Po6
M·Eco98I	AAGCTT	Po6
M·Eco105I	TACGTA	Po6
M·Esp3I	GGT ^{m6} CTC	Ja3
	GAG ^{m6} ACC	
M·EnuDI	GGCC (m ⁵ C)	Lu2,Va1
M·EnuDII	m ⁵ CGCG	Lu2,Ne1
M·EnuDIII	GCGC	Lu2
M·FokI	GGm ⁶ ATG	La6,Lo3,Lu2,Ma8,Nw1
	and Cm ⁶ ATCC	
M·FspI	TGCGCA	Me1
M·FV3	??mC??	Es1 (Frog virus)
M·HaeII	RGCGCY	Lu2,S13
M·HaeIII	GGm ⁵ CC ^b	Lu2,Ma5,S13
M·HapII	CmCGG	Wa1
M·HgaI	GACGC (mC)	Lu2,Nw1
M·HgiAI	GWGCWC	Lu2
M·HgiCI	GGYRCm ⁵ C	Er1
M·HgiCII	GGWCm ⁵ C	Er1
M·HgiEI	GGWCm ⁵ C	Er1
M·HhaI	Gm ⁵ CGC	Ba9,Ca3,Lu2,Sm1,Wu1,Za1
M·HhaII	Gm ⁶ ANTC	Ch1,Ke1,Ma3,Ma4,Sc9,Sm1
M·HincII	GTYRm ⁶ AC	Gr4,Mc8,Ro7 Re2

Methylase^a

M·HindII
M·HindIII
M·HinfI
M·HinPI
M·HjaI
M·HpaI
M·HpaII
M·HphI
M·H2

M·Kpn2I

M·MboI

M·MboII

Mammals

M·MspI

M·MstI

M·MvaI

M·MwoI

M·NaeI

Neurospora

M·NcoI

M·NdeI

M·NgoMVI

M·NgoI

M·NgoPI

M·NgoII

M·NgoAI

M·NgoPII

M·NgoIII

M·NgoIV

M·NgoV

M·NgoVI

M·NgoVII

M·NgoBI

M·NgoBII

M·NlaI

M·NlaIII

M·NlaIV

M·NlaV

M·NlaX

M·PaeR7I

M·PstI

M·PvuII

M·Rth4273I

Specificity^a

GTYR^{m6}AC

^{m6}AAGCTT

G^{m6}ANTC

GCGC

GATATC (^{m6}A)

GTTA^{m6}AC

C^{m5}CGG

T^{m5}CACC

GGCC

GCNGC

GDGCHC

TCCGGA

G^{m6}ATC

GAAG^{m6}A

^{m5}CG^b

^{m5}CCGG^b

TGCGCA

C^{m4}CWGG

GCN₇GC (^{m4}C)

GCCGGC

??^{m5}C??

CCATGG (^mC)

CATATG (^{m6}A)

GGNNCC^b

RGCGCY^b

RG^mCGCY^b

GG^{m5}CC^b

GG^{m5}CC^b

GG^{m5}CC^b

CCGCGG^b

G^{m5}CCGGC^b

GGNN^{m5}CC^b

G^{m6}ATC^b

G^mCWGC^b

T^{m5}CACC^b

GTAN₅^{m5}CTC^b

GGCC

C^{m6}ATG

G^{m5}CCGGC

GGNN^{m5}CC

??^mC??

CTCG^{m6}AG

CTGC^{m6}AG

CAG^{m4}CTG

GTCG^{m6}AC

References

Lu2,Re2,Ro6,Ro7

Lu2,Ro6,Ro7

Ch1,Lu2

Ba9,Lu2

Da1

Br8,Yo3

Lu2,Ma5,Qu1,Wi2,Yo2

Mc8,Ne2,Ne4

La8 (Bacillus phage)

Po6

Mc8

Mc12,Ne4,Ne2

Be6 (Mouse)

Eh2,Je2,Lu2,Nw2,Wa1,Wa5

Me1

Kl3,Po6

Lu2,Lu4

Lu2,Va1

Se2

Lu2,Va1

Si1

Pi5

Ri1

Su2

Ko5,Ri1

Pi3

Su3,Su4

Ko5,Ri1

Ch2,Ko15,Ri1

Ko5,Pi2

Ko5

Ko5

Pi3

Pi3

Mo3

La1,Lu2,Mo3

Lu2

Mo3

La1

Gi3,Th1,Th2

Le1,Wa3,Wa4,Wa6

B11,Ta2

Ba6

<u>Methylase</u> ^a	<u>Specificity</u> ^a	<u>References</u>
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 (m ⁴ 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	m ⁵ 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·TfiI	TCG ^{m6} A	Sa3, Va6
Tetrahymena	??m ⁶ A??	Ca2, Go1
M·XbaI	TCTAG ^{m6} A	Lu2, Mc13, Va1
M·XmaI	CCCGGG (m ⁴ 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- <u>Alu</u> I (AG ^{m5} CT)		AG ^{m4} CT	Bu5
M- <u>Bam</u> HI (GGAT ^{m4} CC)	GG ^{m6} ATCC	GGATC ^{m5} C	La7,Mc10
M- <u>Bst</u> I (GGAT ^m CC) ^c	GG ^{m6} ATCC		Le2
M- <u>Cfr</u> 6I (CAG ^{m4} CTG)		CAG ^{m5} CTG	Bu5
M- <u>Cla</u> I (ATCG ^{m6} AT)	m ⁶ ATCGAT AT ^{m5} CGAT		M9,Mc11,We1
M- <u>Cvi</u> BIII (TCG ^{m6} A)	T ^{m5} CGA		Mc10,Va4
M- <u>Eco</u> RI (GA ^{m6} ATTC)	GAATT ^{m5} C	G ^{m6} AATTC	Br2
M- <u>Eco</u> RII (C ^{m5} CWGG)		C ^{m4} CWGG	Bu4
M- <u>Eco</u> <u>dam</u> (G ^{m6} ATC)	GAT ^{m5} C ^c GAT ^{hm5} C GAT ^{m4} C		Mc10
M- <u>Fok</u> IA (GG ^{m6} ATG) ^c	CATC ^{m5} C	CAT ^{m5} CC	Ne4
M- <u>Hha</u> I (G ^{m5} CGC)	GCG ^{m5} C		Po3,Po4,Sc2
M- <u>Hha</u> II (G ^{m6} ANTC)	GANT ^{m5} C		Ro1
M- <u>Hpa</u> II (C ^{m5} CGG)		m ⁵ CCGG	Mc10
M- <u>Hph</u> I (T ^{m5} CACC)	GGT ^{m6} A		Mc9,Mc10
M- <u>Mbo</u> I (G ^{m6} ATC)	GGT ^{m6} A		Mc10
M- <u>Mbo</u> II (GAAG ^{m6} A)	GAT ^{m5} C		Mc10
M- <u>Msp</u> I (m ⁵ CCGG)	T ^{m5} CTT ^{m5} C	C ^{m5} CGG	Mc10
M- <u>Mva</u> I (C ^{m4} CWGG)	C ^{m5} CWGG m ⁵ C ^{m5} CWGG		Mc10
M- <u>Pvu</u> II (CAG ^{m4} CTG)		CAG ^{m5} CTG	Bu4
M- <u>Eco</u> T2 <u>dam</u> (G ^{m6} ATY)	GAT ^{hm5} C		Ne1
M- <u>Eco</u> T4 <u>dam</u> (G ^{m6} ATC)	GAT ^{hm5} C		Bu5
M- <u>Taq</u> I (TCG ^{m6} A)		T ^{m5} CGA ^c	Do2,Mi1
			Sc4
			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.

<u>Restriction isoschizomer pairs</u> ^{a,b}			
<u>Methylated sequence</u> ^c	<u>Cut by</u>	<u>Not cut by</u>	<u>References</u>
m ⁴ CCGG	<u>MspI</u>	<u>HpaII</u>	Ne1
Cm ⁵ CGG	<u>MspI</u>	<u>HpaII (HapII)</u>	Eh2,Mc11
Cm ⁴ CGG	<u>MspI</u>	<u>HpaII</u>	Bu6
CCm ⁵ CGGG	<u>XmaI (Cfr9I)</u>	<u>SmaI</u>	Bu6
Cm ⁵ CWGG	<u>BstNI (MvaI)</u>	<u>EcoRII</u>	Bu4
Gm ⁶ ATC	<u>Sau3A (FnuEI)</u>	<u>MboI (NdeII)</u>	Ge1,Lu1,Mc9,Ro3
GATm ⁵ C	<u>MboI</u>	<u>Sau3A</u>	Ne4
GATm ⁴ C	<u>MboI</u>	<u>Sau3A</u>	Ne4
GGCm ⁵ C	<u>HaeIII</u>	<u>NgoPII</u>	Su4
GGTACm ⁵ C	<u>KpnI</u>	<u>Asp718I</u>	Mu1
GGTAm ⁵ Cm ⁵ C	<u>KpnI</u>	<u>Asp718I</u>	Ne4
GGWCm ⁵ C	<u>AflII</u>	<u>AvaII (Eco47I)</u>	B3,Ja5,Wh2
RGm ⁶ ATCY	<u>XhoII (BstYI)</u>	<u>MfiII</u>	Mc9,Ne4
Tm ⁵ CCGGA	<u>AccIII</u>	<u>BspMII (MroI)</u>	La2,Sc2
TCm ⁵ CGGA	<u>AccIII</u>	<u>BspMII (MroI)</u>	Sc2
TCCGGm ⁶ A	<u>BspMII (MroI)</u>	<u>AccIII</u>	Ke3,Ne4
TCGCGm ⁶ A	<u>Sbo13I (SalDI)</u>	<u>NruI</u>	Mc11,Ne4
TTm ⁵ CGAA	<u>AsuII</u>	<u>Csp45I</u>	Sc10
CGGWCm ⁵ CG	<u>CspI</u>	<u>RsrII</u>	Qi3
<u>Restriction isomethylator pairs</u> ^{d,e}			
<u>Methylated sequence</u> ^c	<u>methyated by</u>	<u>Not methyated by</u>	<u>References</u>
Tm ⁵ CGA	M.CviBIII (TCGm ⁶ 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	<u>Cvi</u> NY
RGCY	<u>Cvi</u> JI
CATG	<u>Nla</u> III
CCTC	<u>Mnl</u> I
AGCT	<u>Alu</u> I
CCGG	<u>Bsu</u> FI, <u>Bsu</u> QI, <u>Hap</u> II, <u>Hpa</u> II, <u>Msp</u> I
CGCG	<u>Acc</u> II, <u>Bep</u> I, <u>Bst</u> UI, <u>Bsu</u> EII, <u>Fnu</u> DII, <u>Tha</u> I
Gm ⁶ ATC	<u>Dpn</u> I, <u>Nan</u> II, <u>Nmu</u> DI, <u>Nmu</u> EI
GATC	<u>Bce</u> 243I, <u>Bsa</u> PI, <u>Bsp</u> 67I, <u>Bsp</u> AI, <u>Bsp</u> PII, <u>Bsr</u> PI, <u>Bss</u> GII, <u>Bst</u> EIII, <u>Bst</u> XII, <u>Cpa</u> I, <u>Cty</u> I, <u>Cvi</u> AI, <u>Dpn</u> II, <u>Fnu</u> AII, <u>Fnu</u> CI, <u>Fnu</u> EI, <u>Mbo</u> I, <u>Mme</u> II, <u>Mno</u> III, <u>Mos</u> I, <u>Mth</u> I, <u>Nde</u> II, <u>Nfi</u> I, <u>Nla</u> II, <u>Nsi</u> AI, <u>Nsu</u> I, <u>Pfa</u> I, <u>Sau</u> 3A, <u>Sin</u> MI
GCGC	<u>Hha</u> I, <u>Hin</u> PI
GGCC	<u>Bsu</u> RI, <u>Hae</u> III, <u>Ng</u> oPII
GTAC	<u>Cvi</u> QI, <u>Rsa</u> I
TCGA	<u>Taq</u> I, <u>Tfi</u> I, <u>Tth</u> I
TTAA	<u>Mse</u> I
CCNGG	<u>Scr</u> FI
CTNAG	<u>Dde</u> I
GANTC	<u>Cvi</u> BI, <u>Hha</u> II, <u>Hinf</u> I
GGNCC	<u>Cfr</u> 13I, <u>Sau</u> 96I
CCWGG	<u>Aac</u> I, <u>Aor</u> I, <u>Apv</u> I, <u>Atu</u> BI, <u>Atu</u> II, <u>Bin</u> SI, <u>Bsp</u> NI, <u>Bst</u> GII, <u>Bst</u> NI, <u>Cfr</u> 5I, <u>Cfr</u> II I, <u>Eca</u> II, <u>Ecl</u> II, <u>Eco</u> RII, <u>Eco</u> 27I, <u>Eco</u> 38I, <u>Mph</u> I, <u>Mva</u> I, <u>Taq</u> XI
CCSGG	<u>Bcn</u> I, <u>Nci</u> I
GCAGC	<u>Bbv</u> I
GGWCC	<u>Ava</u> II, <u>Bme</u> 216I, <u>Eco</u> 47I, <u>Hgi</u> CII, <u>Hgi</u> EI, <u>Sin</u> I
AGACC	<u>Eco</u> PI
ACCTGC	<u>Bsp</u> MI
CAGCAG	<u>Eco</u> P15
CATCC	<u>Fok</u> I
GAAGA	<u>Mbo</u> II, <u>Ncu</u> I
GAAGAG	<u>Ear</u> I
GAATGC	<u>Bsm</u> I
GACCGA	<u>Taq</u> II
and CACCCA	
GACGC	<u>Hga</u> I
GATGC	<u>Sfa</u> NI
GGATC	<u>Alw</u> I, <u>Bin</u> I
GTCTC	<u>Bsm</u> AI
TCACC	<u>Hph</u> I, <u>Ng</u> oBI
GDGCHC	<u>Bsp</u> 1286I
CYCGRG	<u>Aqu</u> I, <u>Ava</u> I
GRCGYC	<u>Aha</u> II
GRCGYC	<u>Aos</u> II, <u>Bbi</u> II, <u>Ban</u> II
GRGCYC	<u>Hgi</u> JII
GTMKAC	<u>Acc</u> I
GTYRAC	<u>Hin</u> CII

GWGCWC	<u>Hgi</u> AI
RCCGGY	<u>Cfr</u> 10
RGCGCY	<u>Hae</u> II, <u>Ngo</u> PI
RGATCY	<u>Bst</u> YI, <u>Mfi</u> II, <u>Xho</u> II
YGGCCR	<u>Cfr</u> I, <u>Eae</u> I
RGGNCCY	<u>Dra</u> II
AAGCTT	<u>Hind</u> III
ACGCGT	<u>Mlu</u> I
ACTAGT	<u>Spe</u> I
AGATCT	<u>Bgl</u> II, <u>Nci</u> I
AGCGCT	<u>Avi</u> II, <u>Eco</u> 47III
AGGCCT	<u>Stu</u> I
ATCGAT	<u>Ban</u> III, <u>Bsp</u> XI, <u>Cla</u> I
ATGCAT	<u>Nsi</u> I
CAGCTG	<u>Cfr</u> 6I, <u>Pvu</u> II
CATATG	<u>Nde</u> I
CCATGG	<u>Nco</u> I
CCCGGG	<u>Cfr</u> 9I, <u>Sma</u> I, <u>Xma</u> I
CCGCGG	<u>Sac</u> II
CGATCG	<u>Bma</u> DI, <u>Pvu</u> I, <u>Rsh</u> I, <u>Xor</u> II
CGGCCG	<u>Eag</u> I, <u>Xma</u> III
CGTACG	<u>Pfu</u> I, <u>Spl</u> I
CTCGAG	<u>Bsu</u> MI, <u>Bsu</u> RII, <u>Pae</u> R7I, <u>Xho</u> I
CTGCAG	<u>Bsu</u> BI, <u>Pst</u> I, <u>Sfi</u> I
CTTAAG	<u>Afl</u> II
GAATTC	<u>Eco</u> RI, <u>Rsr</u> I, <u>Sso</u> 47I
GACGTC	<u>Aat</u> II
GAGCTC	<u>Sac</u> I, <u>Sst</u> I
GATATC	<u>Eco</u> RV
GCATGC	<u>Sph</u> I
GCCGGC	<u>Mlu</u> 9273II, <u>Nae</u> I
GCGCGC	<u>Bss</u> HII
GCTAGC	<u>Nhe</u> I
GGATCC	<u>Bam</u> HI, <u>Bam</u> FI, <u>Bam</u> KI, <u>Bam</u> NI, <u>Bst</u> I, <u>Bst</u> I, <u>Bst</u> 1503I
GCGGCC	<u>Bbe</u> I, <u>Nar</u> I
GGTACC	<u>Asp</u> 718I, <u>Kpn</u> I
GGGCCC	<u>Apa</u> I
GTCGAC	<u>Rrh</u> 4273I, <u>Sal</u> I
GTGCAC	<u>Apa</u> LI
GTTAAC	<u>Hpa</u> I
TCATGA	<u>Bsp</u> HI, <u>Rsp</u> XI
TCCGGA	<u>Acc</u> III, <u>Bsp</u> MII, <u>Kpn</u> 2I, <u>Mro</u> I
TCGCGA	<u>Ama</u> I, <u>Mlu</u> I9273I
TCGCGA	<u>Nru</u> I, <u>Sal</u> DI, <u>Sbo</u> 13I, <u>Spo</u> I
TCTAGA	<u>Xba</u> I
TGATCA	<u>Atu</u> CI, <u>Bcl</u> I, <u>Bsp</u> XII, <u>Bst</u> GI, <u>Cpe</u> I
TGCGCA	<u>Fsp</u> I
TGGCCA	<u>Bal</u> I
TTCGAA	<u>Asu</u> II, <u>Bst</u> BI, <u>Csp</u> 45I
TTTAAA	<u>Dra</u> I
CCAN ₆ TGG	<u>Pfi</u> MI, <u>Bst</u> XI
CCTNAGG	<u>Mst</u> II
GAAN ₄ TTC	<u>Xmn</u> I
GATN ₄ ATC	<u>Mam</u> I
GCCN ₅ GGC	<u>Bgl</u> I

GCTNAGC	<u>EspI</u>
GGTNACC	<u>BstEII</u> , <u>EcaI</u>
CGGWCCG	<u>CspI</u> , <u>RsrII</u>
GAAN ₆ RTCG	<u>EcoR124</u>
GAAN ₇ RTCG	<u>EcoR124/3</u>
AACN ₆ GTGC	<u>EcoK</u>
AACN ₆ GTRC	<u>StySPI</u>
GAGN ₇ ATGC	<u>EcoE</u>
GAGN ₇ GTCA	<u>EcoA</u>
GAGN ₆ RTAYG	<u>StySBI</u>
TCAN ₇ ATTC	<u>EcoDXXI</u>
TGAN ₈ TGCT	<u>EcoB</u>
TTAN ₇ GTCY	<u>EcoD</u>
CRGCCGGYG	<u>SgrAI</u>
GGCCGGCC	<u>FseI</u>
GCGGCCGC	<u>NotI</u>
GGCCN ₅ GGCC	<u>SfiI</u>