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

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We present in **Table I** an updated list of the sensitivities of 298 restriction endonucleases and 20 DNA methyltransferases to site-specific modification at 4-methylcytosine (^{m4}C), 5-methylcytosine (^{m5}C), 5-hydroxymethylcytosine (^{hm5}C), and 6-methyladenine (^{m6}A) (McC14), four modifications that are common in the DNA of prokaryotes, eukaryotes, and their viruses (Mc2,Mc5,Mc8,Mc11,Ne3,Ne4). In addition, new information is included on restriction endonuclease cleavage at sites modified with 5-hydroxymethyluracil (^{hm5}U).

Knowledge of the sensitivity of restriction endonucleases to site-specific modification can be used to study cellular DNA methylation. Several restriction-modification enzymes share the same recognition sequence specificity, but have different sensitivities to site-specific methylation. **Table II** lists 32 known isoschizomer pairs and one isomethylator pair, along with the modified recognition sites at which they differ.

The data presented here and an additional three other tables are available in printed form or as a text file on a 3.5″ Macintosh diskette. The extra tables include **Table III** which is a list of over 205 characterized DNA methyltransferases. A detailed list of cloned restriction-modification genes has been made by Wilson (Wi4). **Table IV** 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 (Bu9,Mc10, Ne3,Po4), and this sensitivity often differs from that of their restriction endonuclease partners. **Table V** gives a list of restriction systems in this review alphabetized by recognition sequence. 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.

Molecular basis for sensitivity restriction enzymes to methylation

^{m4}C, ^{m5}C, ^{hm5}C, and ^{m6}A are bulky alkyl substitutions in the major groove of DNA. 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. At the molecular level, the inability of restriction enzymes to cut modified DNA can be explained using *Eco*RI and *Eco*RV endonucleases as instructive models. DNA modification can interfere with substrate binding and/or conformational changes of the enzyme: substrate complex.

Based on the *Eco*RI: DNA co-crystal structure (Mc15,Ro8), methylation of either adenine ($G^{m6}AATTC$ or $GA^{m6}ATTC$) perturbs essential hydrogen bond contacts to Glu-144 and Arg-145. Therefore aminomethylation of either adenine inhibits DNA cleavage at the level of *Eco*RI: substrate binding (Br2). In contrast, cytosine ring methylation at $GAATT^{m5}C$ would not be expected to interfere with critical DNA: protein contacts inferred from the X-ray crystal structure (Mc15). Therefore, the reduced rate of *Eco*RI cleavage at $GAATT^{m5}C$ can be attributed to steric distortions of the enzyme:substrate complex during catalysis (He3).

Based upon the X-ray structure of *Eco*RV endonuclease (Wi5), hydrogen bonding of Asn-185 to the first adenine of GATATC is perturbed by 'canonical' methylation at the $G^{m6}ATATC$. The canonical site is the site of methylation by the corresponding methylase in the same restriction system, in this case M·.*Eco*RV. However, *Eco*RV cannot cleave canonically modified $G^{m6}ATATC$ sites because non-productive enzyme: substrate complexes are formed (Ta4,Ne12). Therefore the mechanism by which canonical DNA methylation inhibits cleavage is very different in the cases of *Eco*RI and *Eco*RV endonucleases.

Although DNA modification often results in complete inhibition of restriction enzyme cleavage, a range of rate effects are observed when non-canonically modified DNA is used as a substrate, as listed in the footnotes to **Table I**. Rate effects at ^{m5}C-hemi-methylated restriction endonuclease target sites are listed in Ne10.

Rate of cleavage at methylated restriction sites

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 endonuclease cleavage 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**.

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(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), *Hae*III cannot cut certain GGCC^{m}T sites, where ^{m}T are modified thymine residues (Wi1), and *Msp*I, *Hpa*II, *Sma*I, and *Hha*I are unable to cut DNAs in which bases adjacent to their recognition sequences are modified with hydroxymethyluracil (Ho1). Such methylation-induced 'action at a distance' may be more common than has been previously appreciated. We have tested only a few enzymes for sensitivity to base modifications *outside* their canonical recognition sequences.

DNA modifications other than ^{m4}C, ^{m5}C, ^{hm5}C, ^{hm5}U, and ^{m6}A

The effects of several other site-specific DNA modifications on the rate of restriction endonuclease cleavage, such as 5-bromodeoxycytidine, 5-bromodeoxyuridine, 5-iododeoxycytidine, deoxyinosine, 2-aminopurine, 2,6-diaminopurine, 2-chloroadenosine, 7-deazaguanosine, and deoxynucleotide phosphorothioate deoxynucleotides, are listed elsewhere (Bo1,Be6,Mo4,Br2,Ta5,He4,Gr3,Se4,Vo2).

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 the 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, *Cvi*QI, *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, *Tsp*509I, *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, *Srf*I, *Xho*I and *Xor*II (see **Table I**). Only five enzymes suitable for pulsed field mapping of eukaryotic chromosomes are known to cut ^{m5}CG-modified DNA: *Acc*III, *Asu*II, *Cfr*9I, *Pme*I and *Xma*I.

^{m4}C, ^{m5}C, and ^{hm5}C cytosine modifications

In some cases, a restriction enzyme may differ in 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. RsaI cuts GTA^{m5}C but not GTA^{m4}C. *Kpn*I cuts GGTAC^{m5}C but not GGTAC^{m4}C. *Bst*YI cuts RGAT^{m5}CY but not RGAT^{m4}CY. Similarly, *Cvi*SIII cuts T^{m5}CGA but not T^{hm5}CGA.

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 IV**). 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 GAT^{m4}C, but methylates GAT^{m5}C relatively slowly. Such data is summarized in **Table IV** 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 (Ne13). For example, (i) 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,We1,Ha1). (ii) Protection of a subset of restriction endonuclease cleavage sites by methylation at overlapping methyltransferase/endonuclease targets has also been described (Hu1,Kl1,Ne6,Qi2). This two-step 'cross-protection' strategy has produced over 70 new cleavage specificities, and many more are possible (Ja2,Ka2,Kl1,Ne6). (iii) 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 (Ha2). (iv) 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 reaction to achieve selective DNA cleavage at the ten base pair sequence, CCGGATCCGG (Mc10). (v) Polypyrimidine oligonucleotides in DNA triplexes have been used to selectively mask restriction-modification sites. For example, polypyrimidine triplexes which overlap M·*Taq*I sites have been used to enable selective restriction cleavage (Ma7, Ko9,Fe3). (vi) 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,He2,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 (Wo3) and other systems (Bu2). Appropriate non-restricting strains of *E.coli* (Go2,Kr2,Ra1,Ra2) should be chosen for efficient transformation and cloning of methylated DNA. Other species also have such restriction systems (e.g. Ma2).

Engineered altered methylase specificities

Many methylase genes 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.

Table I. Methylation sensitivity of restriction endonucleases [a]

Restriction enzyme	Recognition sequence	Sites cut	Sites not cut	References
*Aat*I	AGGCCT	?	AGG^{m5}CCT	Ne1
			AGGC^{m5}CT	So3
			AGGC^{m4}CT	Ne1
*Aat*II	GACGTC	?	GACGT^{m5}C	Ne1
			GA^{m5}CGTC	Fo1
*Acc*I	GTMKAC	?	GTMK^{m6}AC [#]	Lu2,Mc3
			GTMKA^{m5}C [b]	
*Acc*II	CGCG	?	^{m5}CGCG	Ga2
*Acc*III	TCCGGA	T^{m5}CCGGA [b]	TCCGG^{m6}A	Ke3,La2,Sc2
		TC^{m5}CGGA [b]		
*Acc*65I	GGTACC	?	GGTAC^{m5}C	Ne5
*Aci*I	CCGC	?	C^{m5}CGC	Fo1
*Afl*I	GGWCC	GGWC^{m5}C	?	Mc11,Wh2
	GGWC^{m4}C [b]			
*Afl*II	CTTAAG	?	^{m5}CTTAAG	Ne1
	CTTA^{m6}AG			
*Afl*III	ACRYGT	?	A^{m5}CRYGT	Ne1
*Age*I	ACCGGT	?	A^{m5}CCGGT	Ne1
		AC^{m5}CGGT		
*Aha*II	GRCGYC [b]	?	GR^{m5}CGYC	Ka2,Hu1
	GRCGY^{m5}C			
*Alu*I	AGCT	?	^{m6}AGCT	Gr5,Mc11,Ne2
			AG^{m4}CT	
			AG^{m5}CT [#]	Hu1,Wo1,Zh1
			AG^{hm5}CT	Bu9
*Alw*I	GGATC	?	GG^{m6}ATC	Ne4
	GGAT^{m4}C			
*Alw*NI	CAGN$_2$CCT	?	CAGN$_2$C^{m5}CT	Ne5
*Alw*44I	GTGCAC	GTGC^{m6}AC	GTG^{m5}CAC	Ne1
*Alw*NI	CAGN$_3$CTG	?	CAGN$_2$C^{m5}CTGG	Bo5
*Ama*I	TCGCGA	TCGCG^{m6}A	?	Mc13
*Aos*II	GRCGYC	?	GR^{m5}CGYC	Eh2,Gr5,Va3
*Apa*I	GGGCCC	?	GGG^{m5}CCC [#]	La9,Gu9
			GGGCC^{m5}C	
*Ape*I	ACGCGT	?	A^{m5}CGCGT	Ne1,Qi2
*Apa*LI	GTGCAC	GTGC^{m6}AC	GTGCA^{m5}C	Fo1,Ho2,Ho3
		GTG^{m5}CAC		Ne1
*Apy*I	CCWGG	C^{m5}CWGG [b]	^{m5}CCWGG	Kl1,Mc11,Ra3
*Aqu*I	CYCGRG	?	^{m5}CYCGRG [#]	Ka7,Ka8
*Asc*I	GGCGCGCC	?	GG^{m5}CGCGCC	Si2
			GGCG^{m5}CGCC	
			GGCGCG^{m5}CC	
			GGCGCGC^{m5}C	
*Ase*I	ATTAAT	ATT^{m6}AAT	?	Ne1
*Asp*MDI	GATC	G^{m6}ATC	?	Ch4
*Asp*700I	GAAN$_4$TTC	GA^{m6}AN$_4$TTC	G^{m6}AAN$_4$TTC	Ne1
		GAAN$_4$TT^{m5}C		
*Asp*718I	GGTACC	GGT^{m6}A^{m5}CC [b]	GGTAC^{m5}C	Mu2,Ne4
			GGTA^{m5}C^{m5}C [b]	
*Asu*I	GGNCC	GGNC^{m5}C	?	Ra4
*Asu*II	TTCGAA	TT^{m5}CGAA	?	Ne1
*Atu*CI	TGATCA	?	TG^{m6}ATCA	Ro3,Sc12
*Ava*I	CYCGRG	C^{m5}CGGG	^{m5}CYCGRG	Eh2,Ne1
			CY^{m5}CGRG	Ka4,Ka7,Mc11
			CTCG^{m6}AG [b]	Ne2
*Ava*II	GGWCC	GGWC^{m4}C [b]	GGW^{m5}CC	Ba3,Ko3
			GGWC^{m5}C	Mc10,Mc11
			GGW^{hm5}C^{hm5}C	Hu1
*Avi*II	TGCGCA	?	TG^{m5}CGCA	Ne1
*Bae*I	ACN$_4$GTAYC	?	ACN$_4$GTYA^{m5}C	Fo1
*Bal*I	TGGCCA	?	TGG^{m5}CCA [#]	Gi1,Gu9
	TGGC^{m5}CA [b]			
*Bam*HI	GGATCC	GGATC^{m5}C	GGAT^{m4}CC [#]	Br8,Dr1,Ha3,Hu1
		GG^{m6}ATCC	GGAT^{m5}CC	La7
		GG^{m6}ATC^{m5}C	GGAT^{hm5}C^{hm5}C	
		GGATC^{m4}C	GGA^{hm5}UCC	Ho1
*Bam*FI	GGATCC	GG^{m6}ATCC	GGAT^{m4}CC	An1,Sh1
*Bam*KI	GGATCC	GG^{m6}ATCC	GGAT^{m4}CC	An1,Sh1
*Ban*I	GGYRCC [b]	GG^{m5}CGCC	?	Co3,Ka2
		GGYRC^{m4}C		

Table I. *continued:*

*Ban*II	GRGCYC	GRGCY^{m5}C	GRG^{m5}CYC	Fo1,Ne2,Ne6
*Ban*III	ATCGAT	?	ATCG^{m6}AT$^{\#}$	Su1
BbeI	GGCGCC	GGCG^{m5}CC GGCGC^{m5}C	GG^{m5}CGCC	Co3,Ne2,Sh2
*Bbi*II	GRCGYC	?	GR^{m5}CGYC	Co3
*Bbr*PI	CACGTG	?	^{m5}CA^{m5}CGTG	Wo1
*Bbs*I	GAAGAC	GAAGA^{m5}C	?	Fo1
*Bbu*I	GCATGC	GCATG^{m5}C	GC^{m6}ATGC	Ne1
*Bbv*I	GCWGC	?	G^{m5}CWGC$^{\#}$	Do1,Ha3,Va5
*Bca*77I	WCCGGW	WC^{m5}CGGW	W^{m5}CCGGW	Sc10
*Bcl*I	TGATCA [b]	TGAT^{m5}CA	TG^{m6}ATCA TGAT^{hm5}CA	Bi4,Br8,Eh3,Ro3 Hu1
*Bcn*I	CCSGG	^{m5}CCSGG	C^{m4}CSGG$^{\#}$	Ja3,Ja6,Kl1
*Bep*I	CGCG	?	^{m5}CGCG	Ku3
*Bfr*I	CTTAAG	?	^{m5}CTTAAG	Wo1
*Bgl*I	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
*Bgl*II	AGATCT [b]	AG^{m6}ATCT GAT^{hm5}UC^{hm5}U	AGAT^{m5}CT AGAT^{hm5}CT	Bi4,Br8,Dr1,Dy1,Eh3 Hu1,Pi6,Ho1
*Bin*I	GGATC	?	GG^{m6}ATC	Bo2
*Bma*DI	CGATCG	CG^{m6}ATCG	CGAT^{m6}CG	Qi2
*Bme*216I	GGWCC	?	GGWC^{m5}C	Ma9
*Bna*I	GGATCC	GG^{m6}ATCC	GGAT^{m4}CC GGAT^{m5}CC$^{\#}$	Ne1
*Bsa*I	GGTCTC	GAGA^{m5}C^{m5}C	GGTCT^{m5}C	Fo1,Ne5
*Bsa*AI	YACGTR	?	YA^{m5}CGTR	Fo1
*Bsa*BI	GATN$_4$ATC	?	GATN$_4$AT^{m5}C G^{m6}ATN4^{m6}AC	Fo1
*Bsa*HI	GRCGYC	?	GR^{m5}CGYC	Fo1
*Bsa*JI	CCNNGG	C^{m5}CNNGG	?	Fo1
*Bsa*WI	WCCGGW	WC^{m5}CGGW	?	Fo1
*Bsg*I	CTGCAC	?	CTGCA^{m5}C	Fo1
*Bst*EI	CGRYCG	?	^{m5}CGRY^{m5}CG	Fo1
*Bst*WI	CGTACG	?	^{m5}CGTA^{m5}CG	Fo1
*Bsl*I	CCN$_7$GG	?	C^{m5}CN$_7$GG	Fo1
*Bsm*I	GAATGC	GAATG^{m5}C	G^{m6}AATGC	Fo1,Ne1
*Bsm*AI	GTCTC	G^{m6}AGAC	GTCT^{m5}C	Fo1,Ne1
*Bsp*DI	ATCGAT	?	AT^{m5}CGAT ^{m6}ATCG^{m6}AT	Fo1
*Bsp*EI	TCCGGA	TC^{m5}CGGA [b]	TCCGG^{m6}A	Fo1
*Bsp*HI	TCATGA	?	TC^{m6}ATGA TCATG^{m6}A	Pa2,Se3 Mc1
*Bsp*MI	ACCTGC	ACCTG^{m5}C	?	Fo1
*Bsp*MII	TCCGGA	TCCGG^{m6}A	T^{m5}CCGGA TC^{m5}CGGA	La2,Sc2
*Bsp*OI	CCWGG	C^{m5}CWGG	?	Sc10
*Bsp*XI	ATCGAT	?	ATCG^{m6}AT	Zi1
*Bsp*XII	TGATCA	?	TG^{m6}ATCA	Zi1
*Bsp*106I	ATCGAT	?	ATCG^{m5}AT$^{\#}$	Ne5
*Bsp*1286I	GDGCHC	GDGCH^{m5}C	GDG^{m5}CHC	Fo1,Ne2,Ne6
*Bsr*BI	GAGCGG	GAG^{m5}CGG [b]	?	Fo1
*Bsr*FI	RCCGGY	?	RC^{m5}CGGY	Fo1
*Bss*HII	GCGCGC [b]	?	G^{m5}CGCGC	Ne4,Qi3
*Bst*I	GGATCC	GG^{m6}ATCC GGATC^{m5}C	GGAT^{m4}CC GGAT^{m5}CC GGATC^{m4}C	Ne4 Ne1
*Bst*BI	TTCGAA TT^{m5}CGAA	? Wo1	TTCG^{m6}AA	Ne4
*Bst*EII	GGTNACC	GGTNA^{m5}C^{m5}C [b] GGTNAC^{m4}C	GGTNA^{hm5}C^{hm5}C Ne1	Hu1,Mc11
*Bst*EIII	GATC [b]	?	G^{m6}ATC	My1,Ro3
*Bst*GI	TGATCA	?	TG^{m6}ATCA	Ro3
*Bst*NI	CCWGG [b]	^{m5}CCWGG [b] C^{m5}CWGG ^{m5}C^{m5}CWGG [b]	^{hm5}C^{hm5}CWGG C^{m4}CWGG	Br8,Gr5,Hu1,Mc11 Ne1,Ro3
*Bst*UI	CGCG	?	^{m5}CGCG	Ne5
*Bst*XI	CCAN$_6$TGG	?	^{m5}CCAN$_6$TGG	Ne2
*Bst*YI	RGATCY	RG^{m6}ATCY RGAT^{m5}CY	RGAT^{m4}CY	Ne4 Ne1
*Bst*1107I	GTATAC	?	GTATA^{m5}C	Fo1
*Bsu*BI	CTGCAG	?	CTGC^{m6}AG$^{\#}$	Ga1,Je1,Sh1,St5

Table I. *continued:*

*Bsu*EI	CGCG	?	^{m5}CGCG#	Ga1,Je1,Sh1,St5
*Bsu*FI	CCGG	?	^{m5}CCGG#	Je1
*Bsu*MI	CTCGAG	?	CT^{m5}CGAG#	Je1
*Bsu*RI	GGCC	?	GG^{m5}CC# [b]	Gu8,Ki2,Ki3
*Bsu*15I	ATCGAT	?	ATCG^{m6}AT#	Ra4
*Bsu*36I	CCTNAGG	?	^{m5}CCTNAGG	Ne5
*Cbi*I	TTCGAA	TTCG^{m6}AA	?	Mu1
*Ccr*I	CTCGAG	?	CTCG^{m6}AG	Ne1
*Cfo*I	GCGC	?	G^{m5}CGC	Eh1
			G^{hm5}CG^{hm5}C	Hu1
*Cfr*I	YGGCCR	?	YGG^{m5}CCR#	Kl1
*Cfr*6I	CAGCTG	?	CAG^{m4}CTG#	Bu9
			CAG^{m5}CTG	
*Cfr*9I	CCCGGG [b]	C^{m5}CCGGG	^{m4}CCCGGG	Bu10
		CC^{m5}CGGG	^{m5}CCCGGG	
			C^{m4}CGGG#	
			CC^{m4}CGGG	
*Cfr*10I	RCCGGY	?	R^{m5}CCGGY#	Bi5,Kl1
			RC^{m5}CGGY	Ne1
*Cfr*13I	GGNCC	?	GGN^{m5}CC#	Bi5,Kl1
*Cla*I	ATCGAT	?	^{m6}ATCGAT	Ca4,Mc11,Mc12,Ne4
			AT^{m5}CGAT [b]	Wo1
			ATCG^{m6}AT#	Mc3
*Cpe*I	TGATCA	?	TG^{m6}ATCA	Fi1,Ro3
*Csp*I	CGGWCCG	CGGWC^{m5}CG	CGGW^{m5}CCG	Mc11
			^{m5}CGGWCCG	
*Csp*45I	TTCGAA	?	TTCG^{m6}AA	Ne4,Sc11
*Cty*I	GATC	?	G^{m6}ATC#	Ri2
*Cvi*AI	GATC	GAT^{m5}C	G^{m6}ATC	Ne1,Xi1,Xi6
*Cvi*AII	CATG	^{m5}CATG	C^{m6}ATG#	Ne1
*Cvi*BI	GANTC	?	G^{m6}ANTC#	Xi3
*Cvi*JI	RGCY	?	RG^{m5}CY#	Sh3,Xi2
*Cvi*PI	CC	C^{m5}C	^{m5}CC#	Xi4
*Cvi*QI	GTAC	GTA^{m5}C	GT^{m6}AC#	Xi5
*Cvi*RI	TGCA	?	TGC^{m6}A#	Ne1
			TG^{m5}CA	
*Cvi*SIII	TCGA	Tm5CGA	TCGm6A #	Ne1
			Thm5CGA	
*Dde*I	CTNAG	?	^{m5}CTNAG#	Ho4,Ne2
		^{hm5}CTNAG		Hu1
			CTNm6AG	Ne1
*Dpn*I	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
*Dpn*II	GATC	?	G^{m6}ATC#	De1,La3,La4,La5,Ma6,Vo1
*Dra*I	TTTAAA	TTTA^{m6}AA	?	Ne1
*Dra*II	RGGNCCY	?	RGGNC^{m5}CY	Sc8
*Drd*I	GACN$_6$GTC	?	GA^{m5}CN$_6$GT^{m5}C	Fo1
*Eae*I	YGGCCR	?	YGG^{m5}CCR#	Ja2,Wh1
			YGGC^{m5}CR	
*Eag*I	CGGCCG	?	CGG^{m5}CCG	Mc11
			^{m5}CGGC^{m5}CG	
*Eam*1105I	GACN$_5$GTC	GA^{m5}CN$_5$GT^{m5}C	?	Fo1
*Ear*I	GAAGAG	CTCTT^{m5}C	G^{m6}AAGAG	Fo1,Ne4
			GAAG^{m6}AG	
			^{m5}CT^{m5}CTT^{m5}C	Ne1
*Eca*I	GGTNACC	?	GGTN^{m6}ACC#	Br2??
*Ecl*XI	CGGCCG	?	^{m5}CGGC^{m5}CG	Qi3
			CGG^{m5}CCG	
*Ecl*136I	GAGCTC	?	GAGCT^{m5}C	Fo1
*Eco*AI	GAGN$_7$GTCA [b]	?	G^{m6}AGN$_7$G^{m}TCA# [b]	Bi2,Co6,Fu2
*Eco*BI	TGAN$_8$TGCT [b]	?	TG^{m6}AN$_{8m}$TGCT # [b]	Bi2,La10,La11
*Eco*DXXI	TCAN$_7$AATC [b]	?	TCAN$_{7m6}$AA^{m}TC # [b]	Pi1
*Eco*EI	GAGN$_7$ATGC [b]	?	G^{m6}AGN$_7$ATGC	Co6,Fu2
*Eco*KI	AACN$_6$GTGC [b]	?	A^{m6}ACN$_6$G^{m}TGC# [b]	Bi2,Bi3,Ka1
*Eco*O109I	RGGNCCY	?	RGGNC^{m5}CY	Sc8
*Eco*PI	AGACC [b]	AGA^{hm5}C^{hm5}C	AG^{m6}ACC#	Ba1,Ba2,Ha4,Re4
*Eco*P15I	CAGCAG [b]	?	CAGC^{m6}AG#	Hu2,Me2
*Eco*RI	GAATTC	GAATT^{hm5}C	G^{m6}AATTC [b]	Mc11,Ne2,Ru1
		GAA^{hm5}U^{hm5}UC	GA^{m6}ATTC#	Br1,Br8,Du1,Ho1
			GAATT^{m5}C [b]	Hu1,Ka3,Ta1

Table I. *continued:*

*Eco*RII	CCWGG	^{m5}CCWGG [b]	^{m4}CCWGG	Ku1,Yo1
	C^{m4}CWGG	Bu8,Na5,Ro3		
			C^{m5}CWGG [#]	Bo7,Mc11
			CC^{m6}AGG	Bu7
			^{hm5}C^{hm5}CWGG	Hu1,Ka3
*Eco*RV	GATATC	GATAT^{m5}C [b]	G^{m6}ATATC [#]	Mc11,Ne2,Wo1
		GATAT^{hm5}C	GAT^{m6}ATC	Fl1,Ho1
*Eco*R124I	GAAN$_6$RTCG [b]	?	GA^{m6}AN$_6$RTCG	Pr2,Pr3
			GAAN$_6$R^{m}TCG	Bi1
*Eco*R124/3I	GAAN$_7$RTCG [b]	?	^{m6}A	Pr1,Pr2
*Eco*T22 I	ATGCAT	?	ATG^{m5}CAT	Ne1
			ATGC^{m6}AT	
*Eco*31I	GGTCTC	?	GGT^{m5}CTC #	Bu8
			Gm6AGACC #	
*Eco*47I	GGWCC	?	GGWC^{m5}C	Ja5
Eco47II	GGNCC	?	GGNC^{m5}C	Po6
*Eco*47III	AGCGCT	^{m6}AGCGCT	AG^{m5}CGCT	Ne1,Ne4
*Eco*57I	CTGAAG	?	CTGA^{m6}AG	Ja8,Po6
			CTTC^{m6}AG	
*Ehe*I	GGCGCC	?	GG^{m5}CGCC	Co2,Ne1
	GGCG^{m5}CC			
			GG^{hm5}CG^{hm5}C^{hm5}C	
*Esp*I	GCTNAGC	GCTNAG^{m5}C	G^{m5}CTNAGC	Ne4
*Esp*3I	CGTCTC	?	^{m5}CGTCTC	Fo1
			GGT^{m5}CTC #	Ja3
			GAG^{m6}ACC #	
*Fnu*4HI	GCNGC	?	G^{m5}CNGC	Gu9,Ko3
			GCNG^{m5}C	
*Fnu*DII	CGCG	?	^{m5}CGCG	Ga1,Ga2,Ne2,Ne6,St6
			CG^{m5}CG	
*Fnu*EI	GATC	G^{m6}ATC [b]	?	Lu1,Ne2
*Fok*I	CATCC	CAT^{m5}CC	GG^{m6}ATG	Po3,Po4,Sc2
		CATC^{m5}C [b]	C^{m6}ATCC	
		CATC^{m4}C	Ne1	
*Fse*I	GGCCGGCC	?	GG^{m5}CCGG^{m5}CC	Ne7
			GGC^{m5}CGGCC	
			GG^{m5}CCGGCC	
*Fsp*I	TGCGCA	?	TG^{m5}CGCA	Ne4
*Fsu*I	GGWCC	?	GGWC^{m5}C	Le1
*Hae*II	RGCGCY [b]	?	RG^{m5}CGCY	Eh2,Gr5,Ka2,Ko3,Mc11,Pi5
			RGCGm5CY	Ne1
			RG^{hm5}CG^{hm5}CY	Hu1
*Hae*III	GGCC	GGC^{m5}C	GG^{m5}CC [#] [b]	Ba3,Ka2,Ko3,Ma5
			GG^{hm5}C^{hm5}C	Hu1
*Hap*II	CCGG	?	C^{m5}CGG [#]	Eh2,Wa1
*Hga*I	GACGC	?	GA^{m5}CGC	Ne1
			GACG^{m5}C	Mc11
*Hgi*AI	GWGCWC	GWGCW^{m5}C	GWG^{m5}CWC	Fo1,Ne2,Wh3
*Hgi*BI	GGWCC	?	GGW^{m5}C^{m5}C	Ra4
*Hgi*CI	GGYRCC	?	GGYR^{m5}CC #	Er1
*Hgi*CII	GGWCC	?	GGWC^{m5}C	Er1
*Hgi*DI	GRCGYC	?	GR^{m5}CGY^{m5}C	Ra4
*Hgi*DII	GTCGAC	?	GT^{m5}CGAC #	Ra4
*Hgi*EI	GGWCC	?	GGWC^{m5}C	Er1
*Hgi*GI	GRCGYC	?	GR^{m5}CGY^{m5}C	Sw1
*Hgi*JII	GGYRCC	?	GGYRC^{m5}C	Wh3
*Hha*I	GCGC	?	G^{m5}CGC [#]	Eh2,Ko3,Sm1
			GCG^{m5}C	Mc11,
			G^{hm5}CG^{hm5}C	Hu1
*Hha*II	GANTC	?	G^{m6}ANTC [#]	
*Hinc*II	GTYRAC	GTYRA^{m5}C	GTYR^{m6}AC [#]	Gr5,Ro7
			GTYRA^{hm5}C	Hu1
*Hind*II	GTYRAC	?	GTYR^{m6}AC [#]	Ro7
			GTYRA^{hm5}C	
*Hind*III	AAGCTT	A^{m6}AGCTT [#]	^{m6}AAGCTT [#]	Br8,Gr5,Ne1,Ro7
		AAGC^{hm5}U^{hm5}U	AAG^{m5}CTT [b]	Ho1,Ne2
			AAG^{hm5}CTT	Hu1,Ka3
*Hin*fI	GANTC	GANT^{m5}C [b]	G^{m6}ANTC	Ch1,Co1,Ne2,Pe1
			GANT^{hm5}C	Hu1
*Hin*PI	GCGC	?	G^{m5}CGC	Mc11,Ne6
*Hpa*I	GTTAAC	GTTAA^{m5}C	GTTA^{m6}AC [#]	Br8,Gr5,Hu1,Yo3
			GTTAA^{hm5}C	Hu1
			G^{hm5}U^{hm5}UAAC	Ho1
*Hpa*II	CCGG	?	^{m4}CCGG	Be3,Bu10,Eh2,Ma5
			^{m5}CCGG [b]	Ko3,Ou1,Wa5

Table I. *continued:*

		$C^{m4}CGG$ [b]	$C^{m5}CGG$ [#]	
			$^{hm5}C^{hm5}CGG$	Hu1
*Hph*I	TCACC	$TCAC^{m5}C$	$T^{m5}CACC$ [#]	Fo1,Mc11,Ne2
			TCAm5CC	
			$GGTG^{m6}A$	
*Kas*I	GGCGCC	?	$GG^{m5}CGCC$	Fo1
*Kpn*I	GGTACC [b]	$GGTA^{m5}CC$	$GGT^{m6}ACC$ [#]	Eh3,Ki4,Mc11
		$GGTAC^{m5}C$	$GGTAC^{m4}C$	Ne1
		$GGTA^{m5}C^{m5}C$ [b]		
		$GGT^{m6}ACC$		
*Kpn*2I	TCCGGA	$TCCGG^{m6}A$	$T^{m5}CCGGA$	Mc1,Ne1
			$TC^{m5}CGGA$	Ne1
*Ksp*I	CCGCGG	?	$^{m5}CCGCGG$	Ne1
			$C^{m5}CGCGG$	Qi2
*Mae*II	ACGT	?	$A^{m5}CGT$ [b]	Mo2
*Mam*I	$GATN_4ATC$	?	$G^{m6}ATN_4{}^{m6}ATC$	St4
*Mbo*I	GATC [b]	$GAT^{m4}C$	$G^{m6}ATC$ [#]	Br5,Ge1,Mc8
		$GAT^{m5}C$ [b]	$GAT^{hm5}C$	Hu1,Ro3
		$GA^{hm5}UC$		Ho1
*Mbo*II	GAAGA	$T^{m5}CTT^{m5}C$ [b]	$GAAG^{m6}A$ [#]	Ba3,Mc11,Mc12,Ne2
		$G^{m6}AAGA$	$GA^{m6}AGA$	
*Mfl*I	RGATCY [b]	?	$RG^{m6}ATCY$	On1
			$RGAT^{m4}CY$	
			$RGAT^{m5}CY$	
*Mlu*I	ACGCGT	$^{m6}ACGCGT$	$A^{m5}CGCGT$	Mc11,Sh1,St5,Qi3
*Mlu*9273I	TCGCGA	?	$T^{m5}CGCGA$	Ne1
*Mlu*9273II	GCCGGC		$G^{m5}CCGGC$	Ne1
$GC^{m5}CGGC$				
*Mme*II	GATC	?	$G^{m6}ATC$	Bo6
*Mnl*I	CCTC	?	$^{m5}CCTC$	Eh3,Mc11
			$^{m5}C^{m5}CT^{m5}C$	
*Mph*I	CCWGG [b]	?	$C^{m5}CWGG$	Ro3
*Mro*I	TCCGGA	$TCCGG^{m6}A$	$T^{m5}CCGGA$	Mc1,Ne1
	$TC^{m5}CGGA$	Ne1		
*Msc*I	TGGCCA	?	$TGGC^{m5}CA$	Fo1
*Msp*I	CCGG [b]	$^{m4}CCGG$	$^{m5}CCGG$ [#]	Eh2,Je2,Va3,Wa1,Wa5
		$C^{m4}CGG$	$^{hm5}C^{hm5}CGG$	Bu10,Hu1
$C^{m5}CGG$				
*Mst*II	CCTNAGG	$^{m5}CCTNAGG$	?	Ne5
*Mth*TI	GGCC	?	$GG^{m5}CC$ [#]	No4
*Mva*I	CCWGG	$C^{m5}CWGG$ [b]	$C^{m4}CWGG$ [#]	Bu8,Ku2
		$^{m5}CCWGG$	$CC^{m6}AGG$ [b]	Gr4,Ku1
			$^{m4}CCWGG$ [b]	
			$^{m5}C^{m5}CWGG$ [b]	Ne1
*Mun*I	CAATTG	?	$CA^{m5}ATTG$ [#]	St8
*Mvn*I	CGCG	?	$^{m5}CGCG$	Ne1
*Nae*I	GCCGGC	?	$G^{m5}CCGGC$	Eh3,Kl1,Mc11,Ne5
			$GC^{m5}CGGC$	
			$GCCGG^{m5}C$	
*Nan*II	$G^{m6}ATC$ [b]	$G^{m6}ATC$	GATC	Pa1,Ne5
		$G^{m6}AT^{m5}C$ [b]	$GAT^{m5}C$	
*Nar*I	GGCGCC	$GGCGC^{m5}C$	$GG^{m5}CGCC$	Ko3,Mc11,Ne5
			$GGCGC^{m4}C$	Ne1
			$GGCGC^{m5}C$	
			$GG^{hm5}CG^{hm5}Ch^{hm5}C$	
*Nci*I	CCSGG	$^{m5}CCSGG$	$C^{m4}CSGG$	Br8,Ko3,Mc11
			$C^{m5}CSGG$ [b]	
*Nco*I	CCATGG	$CC^{m6}ATGG$	$^{m4}CCATGG$ [b]	Kl1,Ne2,Ne4
			$^{m5}CCATGG$	
*Ncr*I	AGATCT	$AG^{m6}ATCT$ [b]	?	Qi1
*Ncu*I	GAAGA	?	$GAAG^{m6}A$	Mc13
*Nde*I	CATATG	$^{m5}CATATG$ [b]	^{m6}A	Be4,Mc11
*Nde*II	GATC	$GAT^{m5}C$ [b]	$G^{m6}ATC$	Mc9
*Ngo*I [b]	RGCGCY	?	$RG^{m5}CGCY$	Ko3,Ko5
*Ngo*II [b]	GGCC	?	$GG^{m5}CC$ [#]	Ko3,Ko5
			$GGC^{m5}C$ [b]	Su3,Su4
*Ngo*BI [b]	TCACC	?	$T^{m5}CACC$	Pi3,Pi4
*Ngo*MI	GCCGGC	?	$GC^{m5}CGGC$	Fo1
*Nhe*I	GCTAGC	?	$GCTAG^{m5}C$	Kl1,Mc11,Ne2
*Nla*III	CATG	?	$C^{m6}ATG$ [#]	La1,Mo3
			$^{m5}CATG$	Zh2
*Nla*IV	GGNNCC	?	$GGNN^{m4}CC$	Ne1
*Nmu*DI	$G^{m6}ATC$ [b]	$G^{m6}ATC$	GATC	Pa1
*Nmu*EI	$G^{m6}ATC$ [b]	$G^{m6}ATC$	GATC	Pa1
*Not*I	GCGGCCGC	$GCGGCCG^{m5}C$	$GCGG^{m5}CCGC$	Mc11

Table I. *continued:*

			GCGGC^{m5}CGC	St5,Qi2
*Nru*I	TCGCGA	TCG^{m5}CGA	T^{m5}CGCGA	Ne1,Qi3
			TCGCG^{m6}A	Ne2
*Nsi*I	ATGCAT	TG^{m5}CATA	ATGC^{m6}AT	Be5,Wo1
*Nsp*I	RCATGY	?	RC^{m6}ATGY	Ne1
			R^{m5}CATGY	Ne1
*Nsp*BII	CMGCKG	C^{m5}CGCKG	?	Ne1
*Pfl*MI	CCAN$_5$TGG	?	C^{m4}CAN$_5$TGG	Ne1
			C^{m5}CAN$_5$TGG	St7
*Pfa*I	GATC	G^{m6}ATC	?	Ro3
*Pfu*I	CGTACG	?	CGTA^{m5}CG	Ne1
*Pae*R7I	CTCGAG	?	CTCG^{m6}AG$^{\#}$	Gi3
			CT^{m5}CGAG [b]	Gh1
*Pme*I	GTTTAAAC	GTTTAAA^{m5}C	?	Fo1
*Pml*I	CACGTG	?	CA^{m5}CGTG	Fo1
*Ppu*AI	CGTACG	?	CGTA^{m5}CG	Ne1
*Ppu*MI	RGGWCCY	?	RGGWC^{m5}CT	Fo1
*Pst*I	CTGCAG	?	^{m5}CTGCAG [b]	Do1,Gr5,Mc11,Ne2
			CTGC^{m6}AG$^{\#}$	
			C^{hm5}UGCAG	Ho1
*Pvu*I	CGATCG [b]	CG^{m6}ATCG	CGAT^{m4}CG	Br8,Bu7,Eh3
			CGAT^{m5}CG	
*Pvu*II	CAGCTG	?	CAG^{m4}CTG$^{\#}$	Br8,Bu9,Do1
			CAG^{m5}CTG [b]	Eh3,Ja3,Ro1
*Rfl*FI	GTCGAC	?	GTCG^{m6}AC	Mo5
*Rfl*FII	AGTACT	?	AGT^{m6}ACT	Mo5
*Rrh*4273I	GTCGAC	?	GTCG^{m6}AC	Ba6
*Rsa*I	GTAC [b]	GTA^{m5}C [b]	GT^{m6}AC	Eh3,Fo1,Ne1,Ne4,Ne5
			GTA^{m4}C	Wo2
*Rsh*I	CGATCG	CG^{m6}ATCG	?	Ly1
*Rsp*XI	TCATGA	?	TC^{m6}ATGA	Pa2
			TCATG^{m6}A	Ne4
*Rsr*I	GAATTC	?	G^{m6}AATTC	Mc11
	GA^{m6}ATTC$^{\#}$ [b]	Ba5		
*Rsr*II	CGGWCCG	?	^{m5}CGGWCCG	Mc11,Qi3
			CGGW^{m5}CCG	
			CGGWC^{m5}CG	
*Sac*I	GAGCTC	G^{m6}AGCTC	GAG^{m5}CTC	Mc11
		GAGCT^{m5}C	Fo1	
*Sac*II	CCGCGG	?	^{m5}CCGCGG	Kl1,Ne2
*Sal*I	GTCGAC	GTCGA^{m5}C	GT^{m5}CGAC [b]	Br8,Eh2,Lu2,Qi1
			GTCG^{m6}AC$^{\#}$	Mc3,Ro4,Ro5,Va4
			G^{hm5}UCGAC	Ho1
*Sal*DI	TCGCGA	TCGCG^{m6}A	T^{m5}CGCGA	Mc13,Ne1,Qi3
*Sau*3AI	GATC [b]	G^{m6}ATC	GAT^{m5}C$^{\#}$ [b]	Dr1,Eh2,Ja3,Mc3,Ro3,Se1
		GA^{hm5}UC	GAT^{m4}C	Ho1,Ne5
			GAT^{hm5}C	Hu1
*Sau*96I	GGNCC	?	GGN^{m5}CC$^{\#}$	Ko3,Ne2,Pe1
			GGNC^{m5}C	
			GGN^{hm5}C^{hm5}C	Hu1
*Sau*3239I	CTCGAG	?	CTCG^{m6}AG$^{\#}$	Ra4
*Sbo*13I	TCGCGA	TCGCG^{m6}A	T^{m5}CGCGA	Mc11,Ne1
*Sca*I	AGTACT	AGTA^{m5}CT	?	Wo1
*Scr*FI	CCNGG	^{m5}CCNGG	C^{m5}CNGG	Da4,Mc11,Ne2
			C^{m4}CNGG	Ne1
*Sfa*NI	GATGC	GATG^{m5}C	G^{m6}ATGC	Mc11,Po4
*Sfi*I	GGCCN$_5$GGCC	GG^{m5}CCN$_5$GG^{m5}CC [b]	GGC^{m5}CN$_5$GGCC	Mc11,Qi2
		GGCCN$_5$GGC^{m5}C		
*Sfl*I	CTGCAG	?	CTGC^{m6}AG	Br8
*Sgr*AI	CRCCGGYG	?	CRC^{m5}CGGYG	Ta3
*Sin*I	GGWCC	?	GGW^{m5}CC$^{\#}$	Ka5,Ka6
*Sma*I	CCCGGG	C^{m5}CCGGG	^{m4}CCCGGG	Br8,Bu10,Eh2,Ga4
			^{m5}CCCGGG [b]	Ja3,Ka7,Mc3,Qu1
			C^{m4}CCGGG [b]	
			CC^{m4}CGGG	
			CC^{m5}CGGG [b]	
*Sna*BI	TACGTA	?	TA^{m5}CGTA	Fo1,Ya1
			T^{m6}ACGT^{m6}A	
*Sno*I	GTGCAC	?	GTG^{m5}CA^{m5}C	Ho3,Wo1
*Spe*I	ACTAGT	?	^{m6}ACTAGT	Ho2
			A^{m5}CTAGT	Wo1
*Sph*I	GCATGC	GCATG^{m5}C	GC^{m6}ATGC	Mc11,Mo3,Ne2
		G^{hm5}CATG^{hm5}C		

Table I. *continued:*

*Spl*I	CGTACG	CGT^{m6}ACG	CGTAm5CG	Ne1,Ne4,Qi3
*Spo*I	TCGCGA	TCGCG^{m6}A	T^{m5}CGCGA TCG^{m5}CGA	Ne1,Ne4
*Srf*I	GCCCGGGC	?	G^{m5}CCCGGGC GC^{m5}CCGGGC GCC^{m5}CGGGC GCCCGGG^{m5}C	Ma11
*Sso*I	GAATTC	?	G^{m6}AATTC$^{\#}$	Ni4
*Sso*II	CCNGG	?	C^{m5}CNGG ^{m5}CCNGG	Vi1 Gr4
*Ssp*RFI	TTCGAA	?	TTCG^{m6}AA	Li1
*Sst*I	GAGCTC	?	GAG^{m5}CTC GAG^{hm5}CT^{hm5}C	Br8,Ro1 Hu1
*Sst*II	CCGCGG	?	^{m5}CCGCGG C^{m5}CGCGG	Ne5 Ne5
*Sts*I	GGATG	?	GG^{m6}ATG$^{\#}$ C^{m6}ATCC$^{\#}$	Ki5
*Stu*I	AGGCCT	?	AGG^{m5}CCT AGGC^{m5}CT AGGC^{m4}CT	Ca4,Mc11 So3 Ne1
*Sty*SBI	GAGN$_6$RTAYG [b]	?	G^{m6}AGN$_6$R^{m}TAYG$^{\#}$ [b]	Na1,Na2
*Sty*SPI	AACN$_6$GTRC [b]	?	A^{m6}ACN$_6$G^{m}TRC$^{\#}$ [b]	Na1,Na2
*Taq*I	TCGA	T^{m5}CGA [b] T^{hm5}CGA [b]	TCG^{m6}A$^{\#}$ Hu1	Gr5,Hu1,Mc3,Va3
*Taq*II CACCCA	GACCGA	?	G^{m6}ACCGA	Ne4
*Taq*XI C^{m5}CWGG	CCWGG	^{m5}CCWGG	?	Gr1
*Tfi*I	GAWTC	GAWT^{m5}C	?	Fo1
*Tfl*I	TCGA	?	TCG^{m6}A	Sa3,Va6
*Tha*I	CGCG	^{m5}CGCG	^{m5}CGCG ^{hm5}CG^{hm5}CG	Ga1,Ne1 Hu1
*Tth*III I	GACN$_3$GTC	GA^{m5}CN$_3$GTC GACN$_3$GT^{m5}C	?	Fo1
*Tth*HBI	TCGA	T^{m5}CGA	TCG^{m6}A$^{\#}$	Sa3
*Tsp*509I	AATT	?	^{m6}AATT	Fo1
*Xba*I	TCTAGA	?	TCTAG^{m6}A$^{\#}$ T^{m5}CTAGA [b] T^{hm5}CTAGA	Mc13,We1 Gr5,Hu1,Ne2
*Xcy*I	CCCGGG	?	C^{m4}CCGGG$^{\#}$	Wi6
*Xho*I	CTCGAG [b]	?	CT^{m5}CGAG CTCG^{m6}AG ^{m5}CTCGAG	Br8,Eh2,Eh3,Ka7 Mc3,Va3
*Xho*II	RGATCY	RG^{m6}ATCY	RGAT^{m5}CY [b]	Br8
*Xma*I	CCCGGG	CC^{m5}CGGG [b]	^{m4}CCCGGG ^{m5}CCCGGG C^{m4}CCGGG CC^{m4}CGGG	Bu10,Yo5,Yo6
*Xma*III	CGGCCG	?	CGG^{m5}CCG	Gu9,Ne2
*Xmn*I	GAAN$_4$TTC	GA^{m6}AN$_4$TTC	G^{m6}AAN$_4$TTC GAAN$_4$TT^{m5}C [b]	Mc11,Ne2
*Xor*II	CGATCG	?	CGAT^{m5}CG CG^{m6}ATCG [b] ^{hm5}CGAT^{hm5}CG	Br8,Eh2 Hu1,Sm4

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; hm5U=hydroxymethyluracil; ^{m}C= methylcytosine, N4 or C5-methylcytosine unspecified; ^{m6}A= N6-methyladenine. Nomenclature is according to (Sm2) and (Co4).

b. *Acc*I nicks slowly in the unmethylated strand of the hemi-methylated sequence GTMKA^{m5}C. *Acc*I cuts slowly at hemimethylated GTMKA^{m5}C (Ne10).
*Acc*III cuts slowly at T^{m5}CCGGA and T^{m5}CCGGA (Sc10).
*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 (Mu2) 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 (Di2).
*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).
*Bsp*EI cleavage slowed by TC^{m5}CGGA (Fo1).

*Bsr*BI cleavage slowed by GAG^{m5}CGG (Fo1).
*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 (Le3).
*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 Bu10 for rate effects.
*Cla*I cuts slowly at hemimethylated AT^{m5}CGAT (Ne10).
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*AI, *Eco*BI, *Eco*DI, *Eco*EI, *Eco*DXXI, *Eco*KI are Type I restriction endonucleases. ^{m}T represents a 6-methyladenine in the complementary strand.
*Eco*PI is a Type III restriction endonuclease (Ba1,Ba2,Ha4).
*Eco*P15I 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 does not cleave some DNA molecules that carry only a single site. However, oligonucleotides containing the EcoRII site can be used to transactivate sites that are resistant to cleavage (Re5). *Eco*RII iisoschizomers that are sensitive to C^{m5}CWGG include *Atu*BI, *Atu*II, *Bst*GII, *Bin*SI, *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*R124I and *Eco*R124/3I are Type I restriction endonucleases. ^{m}T represents a 6-methyladenine in the complementary strand.
*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·FokIA in ref Po4.
*Hae*II shows a reduced 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.
*Hin*fI 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 (Co1,Gr5,Ne5,Ne10). However, the rate difference between unmethylated and fully methylated *Hin*fI sites is only about ten-fold (Hu1,Ne5,Pe1).
*Hin*dIII cuts slowly at hemimethylated AAG^{m5}CTT (Ne10).
*Hpa*II nicking in the unmethylated strand of the hemi-methylated sequence ^{m5}CCGG/CCGG is in dispute (Be3,Bu10,Ko3). HpaII cuts hemimethylated mCCGG fifty times slower and fully methylated mCCGG 3000 times slower than unmethylated DNA (Ko3). See reference (Bu10) for *Hpa*II rate effects.
*Kpn*I sensitivity to hemi-methylated GGTA^{m5}CC and GGTAC^{m5}C sites has been reported. *Kpn*I cuts ^{m5}C-substituted phage XP12 DNA (Ne4) but cuts slowly at hemimethylated GGTA^{m5}C^{m5}C (Ne10).
*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, *Hac*I, *Meu*I, MkrAI, *Mme*II, *Mno*III, *Mos*I, *Msp*67II, *Mth*I, *Mth*AI, *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 (Gr5).
*Mfl*I cuts slowly at ^{m6}AGATCY sites (On1).
Mammalian methylase is the ^{m5}CG methyltransferase from *Mus musculus*. (mouse) (Be7).
*Msp*I cuts the hemi-methylated sequence C^{m5}CGG/CCGG (Wa5) and C^{m4}CGG/CCGG duplexes (Bu10). *Msp*I cuts very slowly at GGC^{m5}CGG (Bu6). 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 (Ku1). *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 (Gu4). *Ngo*PII, *Ngo*II and *Ngo*SI may be the same. *Ngo*PIII may be *Ngo*III.
*Ngo*II 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).
*Pst*I cuts slowly at hemimethylated ^{m5}CTG^{m5}CAG (Ne10).
*Pvu*II cuts slowly at hemimethylated ^{m5}CAG^{m5}CTG (Ne10).
*Rsa*I cuts the fully ^{m5}C-substituted phage XP12 DNA (Ne5), [contradicted by (Fo1)] but does not cut *Chlorella* virus NY2A DNA, which is modified at GT^{m6}AC (Ne4,Xi1). DNA from *Rhodobacter 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.
*Sal*I cuts slowly at hemimethylated GT^{m5}CGAC (Ne10).
*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 (Bu10,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 (Bu10).
*Spe*I cuts slowly at hemimethylated A^{m5}CTAGT (Ne10).
*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 (Ne5,Ne10).
*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 Bu10 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).
*Xor*II, according to the BRL-Gibco catalog, may cut CG^{m6}ATCG.

Table II. Isoschizomer pairs that differ in their sensitivity to sequence-specific methylation.

Methylated sequence[c]	Restriction isoschizomer pairs [a,b] Cut by	Not cut by	References
^{m5}CATG	*Cvi*AII	*Nla*III	Zh2
^{m4}CCGG	*Msp*I	*Hpa*II	Bu10
C^{m5}CGG	*Msp*I	*Hpa*II,*Hap*II	Eh2,Mc11
C^{m4}CGG	*Msp*I	*Hpa*II	Bu10
CC^{m5}CGGG	*Cfr*9I,*Xma*I	*Sma*I	Bu10
^{m5}CCTNAGG	*Mst*II	*Bsu*36I	Ne5
C^{m5}CWGG	*Bst*NI,*Mva*I	*Eco*RII [d]	Bu8
^{m5}CCWGG	*Apy*I,*Eco*RII,*Mva*I	*Apy*I	Ke1,Ku1,Ne3,Yo1
CG^{m6}ATCG	*Pvu*I	*Xor*II	Bi3,Br8,Sm4
GAAN$_4$TT^{m5}C	*Asp*700I	*Xmn*I	Ne1,Ne2
GA^{m5}CN$_6$GT^{m5}C	*Tth*III	*Drd*I	Fo1
GAGCT^{m5}C	*Sac*I	*Ecl*136II	Qi3,Fo1
G^{m6}ATC	*Fnu*EI,*Sau*3AI	*Mbo*I,*Nde*II	Ge1,Lu1,Mc9,Ro3
GAT^{m5}C	*Mbo*I	*Sau*3AI	Ne4
GAT^{m4}C	*Mbo*I	*Sau*3AI	Ne4
GGC^{m5}C	*Hae*III	*Ngo*II	Su4
GGNC^{m5}C	*Asu*I	*Sau*96I	Ko3
GTG^{m5}CAC	*Apa*LI	*Alw*44	Ne1
GGTAC^{m5}C	*Kpn*I	*Asp*718I	Mu2
GGTA^{m5}C^{m5}C	*Kpn*I	*Asp*718I	Ne4
GGWC^{m5}C	*Afl*I	*Ava*II,*Eco*47I	Ba3,Ja5,Wh2
RG^{m6}ATCY	*Bst*YI,*Xho*II	*Mfl*I	Mc9,Ne4,On1
RGAT^{m5}CY	*Bst*YI	*Xho*II	Ne4,On1
T^{m5}CCGGA	*Acc*III	*Bsp*MII,*Kpn*2I,*Mro*I	La2,Sc2
TC^{m5}CGGA	*Acc*III	*Bsp*MII,*Kpn*2I,*Mro*I	Sc2
TCCGG^{m6}A	*Bsp*MII,*Kpn*2I,*Mro*I	*Acc*III	Ke3,Ne4
T^{hm5}CGA	*Taq*I	*Cvi*SIII	Mc14
TCGCG^{m6}A	*Ama*I,*Sal*DI,*Sbo*13I,*Spo*I	*Nru*I	Mc11,Mc13,Ne4
TCG^{m5}CGA	*Nru*I	*Spo*I	Ne1,Qi1
TT^{m5}CGAA	*Asu*II	*Bst*BI,*Csp*45I	Wo1
TTCG^{m6}AA	*Cbi*I	*Bst*BI,*Csp*45I,*Ssp*RFI	Li1,Mu1,Sc11,Wo1
CGGWC^{m5}CG	*Csp*I	*Rsr*II	Qi3

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

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