SUPPLEMENTARY METHODS

Classifier Generation and Supervised Learning Methods

We have previously reported on the use of pattern recognition and a supervised learning strategy to develop a predictive rule based on a set of DNA sequence patterns that discriminate methylation-prone (MP) and methylation-resistant (MR) sequences (1). The training set consisted of sequences representing 4kb genomic windows encompassing nine MP and nine MR CpG islands (1). The approach consisted of 3 steps.

A general-purpose pattern recognition algorithm (described in (2,3)) was used to identify common sequence patterns within the training CpG islands. The algorithm treats multiple sequence comparisons as an evolutionary distance problem in which the goal is to derive the most likely ancestor that could have given rise to a set of sequences. This is referred to as the "minimum weight common mutated sequence" (MWCMS) model. Given a set of input sequences, the model seeks to mutate every input sequence to the same *a priori* unknown sequence using the operations of insertion, deletion, and substitution. Weights are assigned for each operation, and the total weight associated with all mutations is to be minimized. The method allows for non-consecutive sequence strings with various physical constraints (minimum length, distance from center, etc.) and can be set to return the longest (or some preset length) common exact-match sequence string. For this study, the criteria were set to return exact match sequence patterns 7-12 bp in length, allowing N for any base pair substitution, with control on the frequency of such substitutions. This process identified thousands of patterns of 7-12bp in the training sample.

The identified DNA patterns were then input into a machine learning environment consisting of a feature selection algorithm (involving a combinatorial decision tree analysis (4))

coupled with an optimization-based discrete support vector machine classification engine, DAMIP (described in 5-9). DAMIP has several distinct features, including the ability to classify any number of distinct groups, the ability to incorporate heterogeneous types of attributes as input, a high-dimensional data transformation that reduces noise and errors in biological data, the ability to incorporate constraints to limit the misclassification rate, a reserved-judgment region that provides a safeguard against over-training, and successive multi-stage classification capability to handle data points placed in the reserved judgment region. DAMIP has been shown to be a powerful supervised learning approach in predicting various biomedical and bio-behavior phenomena (1,10-12).

The computational design used the 'wrapper approach', where the feature selection algorithm was coupled directly to the DAMIP classification module. In this approach, the feature selection algorithm selects a subset of the DNA sequence patterns. An attribute vector is then formed from the frequency of occurrence of these patterns in each CpG island sequence in the training set, which then serve as the attribute input into the DAMIP classification engine. The accuracy of the resulting classifier is estimated via 10-fold cross validation. This process is repeated with the feature selection algorithm selecting a new subset of patterns, and the DAMIP engine returning the corresponding classifier and associated 10-fold cross-validation accuracy. Thus, at each step, guided by the estimated accuracy (as a measure of goodness), the machine 'learns' as the feature selection algorithm searches through the space of possible subsets for an improved feature set (*i.e.* that which provides improved cross-validation accuracy). The process continues until a pre-set maximum number of iterations is reached, or a minimum correct classification percentage is achieved. The solution at termination provides the current-best discriminatory feature set with the associated classification rule returned from the DAMIP

module. In this case, we set the maximum number of iterations at 100,000 and the minimum classification accuracy at 90%. The system returned a classification rule with a set of seven discriminatory patterns (TCCCCCNC, TTTCCTNC, TCCNCCNCCC, GGAGNAAG, GAGANAAG, GCCACCCC, GAGGAGGNNG) that achieved an accuracy of 89% in the 10-fold cross-validation tests. We refer to this classification rule as PatMAn, for Pattern-based Methylation Analysis.

To generate the SUPER-PatMAn classifier, attribute vectors based on the frequencies of the same 7 sequence patterns noted above and SUZ12 binding status (positive for enrichment, negative for enrichment, or no data/uninformative) for each CpG island in the training set were used as direct input into the DAMIP classification engine. To facilitate direct comparison of the classification accuracy resulting from the two sets of discriminatory patterns (7 patterns, versus 7 patterns + SUZ12), the same 9MP and 9MR CpG islands were used as the training set. SUPER-PatMAn achieved an accuracy of 83% in 10-fold cross-validation tests. The PatMAn and SUPER-PatMAn classifiers were then applied to genomic sequences corresponding to CpG islands derived from the entire genome (n=37,530).

Annotation of CpG islands for SUZ12 binding status. SUZ12 ChIP-chip data from human embryonic stem cells (13) was obtained from http://www.ebi.ac.uk/arrayexpress in the form of raw probe signal intensities for 115 arrays containing a total of 4.5×10^6 60-mers spaced at ~350 bp intervals and covering ~90% of the non-repetitive fraction of the human genome. Custom PERL programs were utilized to $\log_2$ transform probe signal intensity ratios, calculate the mean for each microarray, subtract the difference between the mean and zero from each probe value, and sort probes by chromosome and start position. SUZ12 enriched and non-enriched regions

were identified with a modified version of the PERL-implementation of the ChIPOTle program (14). This analysis calculated chromosome-specific background standard deviation values by analyzing negative probe values since enriched regions in ChIP-chip experiments should have positive probe values. Using a sliding window (1,000bp window, 225bp step), window p-values were calculated, a multiple testing-corrected significance threshold was calculated, significant windows were identified, and adjacent significant windows were collapsed into a single enriched region. Additional criteria filters were implemented that required that a minimum of 2 probes be present per window for the window to be considered informative (although the majority had at least 3), and that 2 probes within the window have values ≥ 2*background standard deviation. This analysis identified 4,350 SUZ12-enriched regions of average length = 1,313bp.

To annotate CpG islands for SUZ12 occupancy status, CpG island were extracted from the human genome (UCSC HG17; criteria: length ≥ 500bp, GC content ≥ 55%, and CpG Obs/Exp ≥ 0.65) and assessed for proximity to enriched and non-enriched SUZ12 regions. CpG islands that were overlapping or within 1kb of a SUZ12-enriched region were considered SUZ12-enriched. Non-enriched CpG islands were then assessed for proximity (within 1kb) to SUZ12 non-enriched regions. Remaining CpG islands that were not within 1kb of either enriched or non-enriched region had insufficient SUZ12 binding data and were labeled as uninformative. These analyses allowed for the annotation of SUZ12 binding data for 93% of CpG islands in the genome, Based on this analysis there were 3,642 SUZ12 (+) CpG islands, 31,238 SUZ12 (-) CpG islands, and the remaining 2,650 had insufficient data.

Similar analyses were performed to determine CTCF occupancy status of CpG islands. Genome-wide CTCF binding has been previously reported (15). Based on criteria established by Kim et al. (15), additional criteria filters were implemented in the ChIPOTle analysis that

required that a minimum of 4 probes per window for the window to be considered informative, and that 4 probes within the window have values ≥ 2.5*background standard deviation.

Functional annotation of gene ontology terms. The **D**atabase for **A**nnotation, **V**isualization and **I**ntegrated **D**iscovery (**DAVID**) Bioinformatics Database (http://david.abcc.ncifcrf.gov) (16) was utilized to identify gene ontology and functional annotation terms significantly enriched among MP CpG islands. Gene symbols corresponding to 63 CpG islands methylated in at least 2 of 3 independent DNMT1-overexpressing clones was used as input. Program settings were as follows: Homo sapiens, Gene Ontology Molecular Function Term level 2, Protein Domains InterPro name, Functional Categories SP_PIR_Keywords. Data analysis and filtering included the consolidation of redundant terms with retention of that with the lowest p-value and exclusion of categories that were non-informative (e.g. disease mutations, alternative splicing), occurred at less than 5%, or had p-values >0.01.

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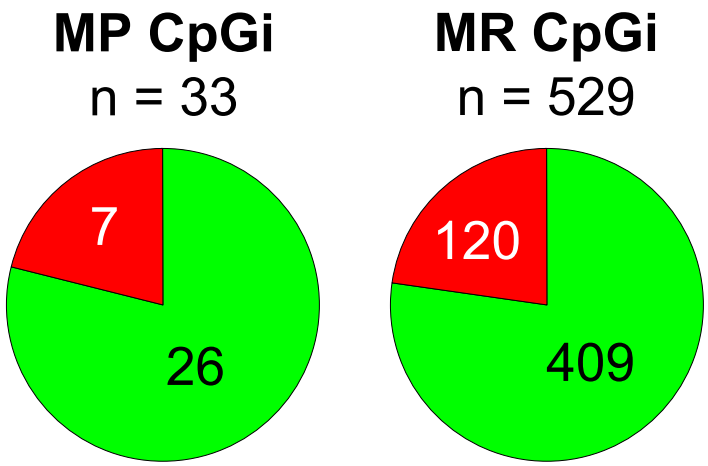
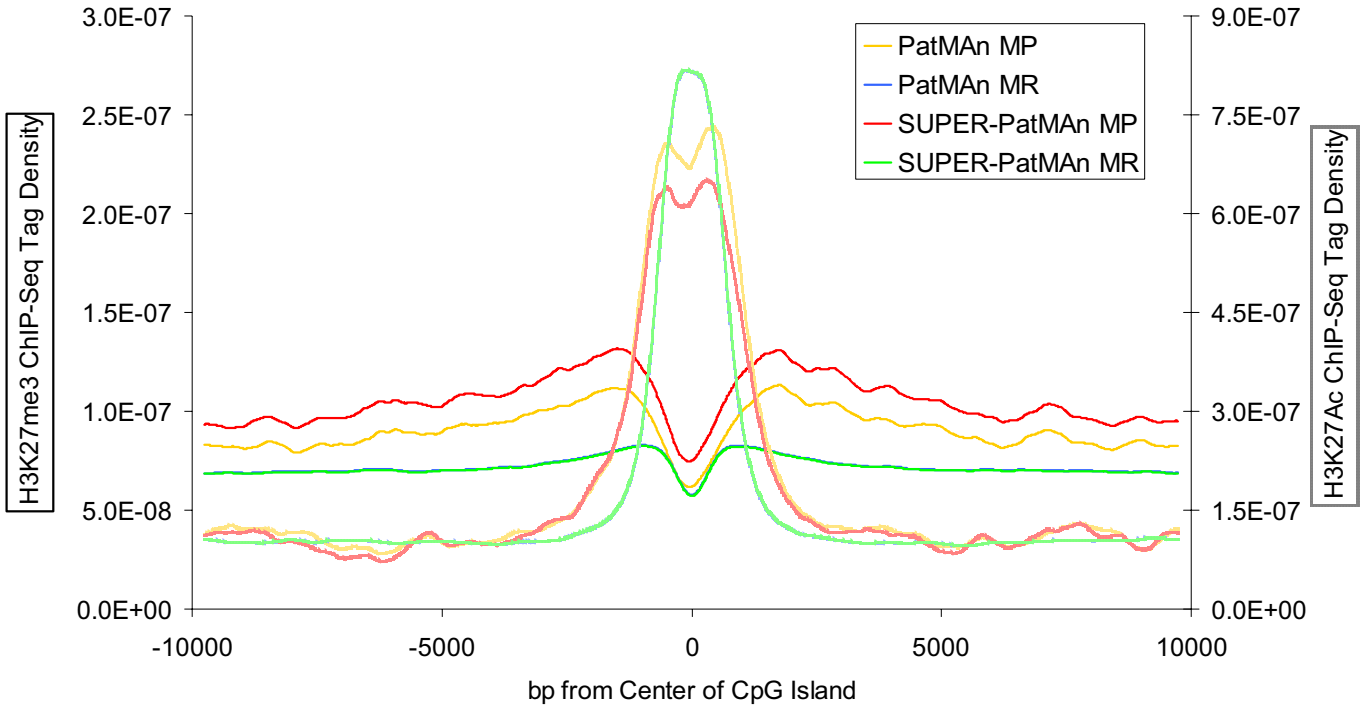
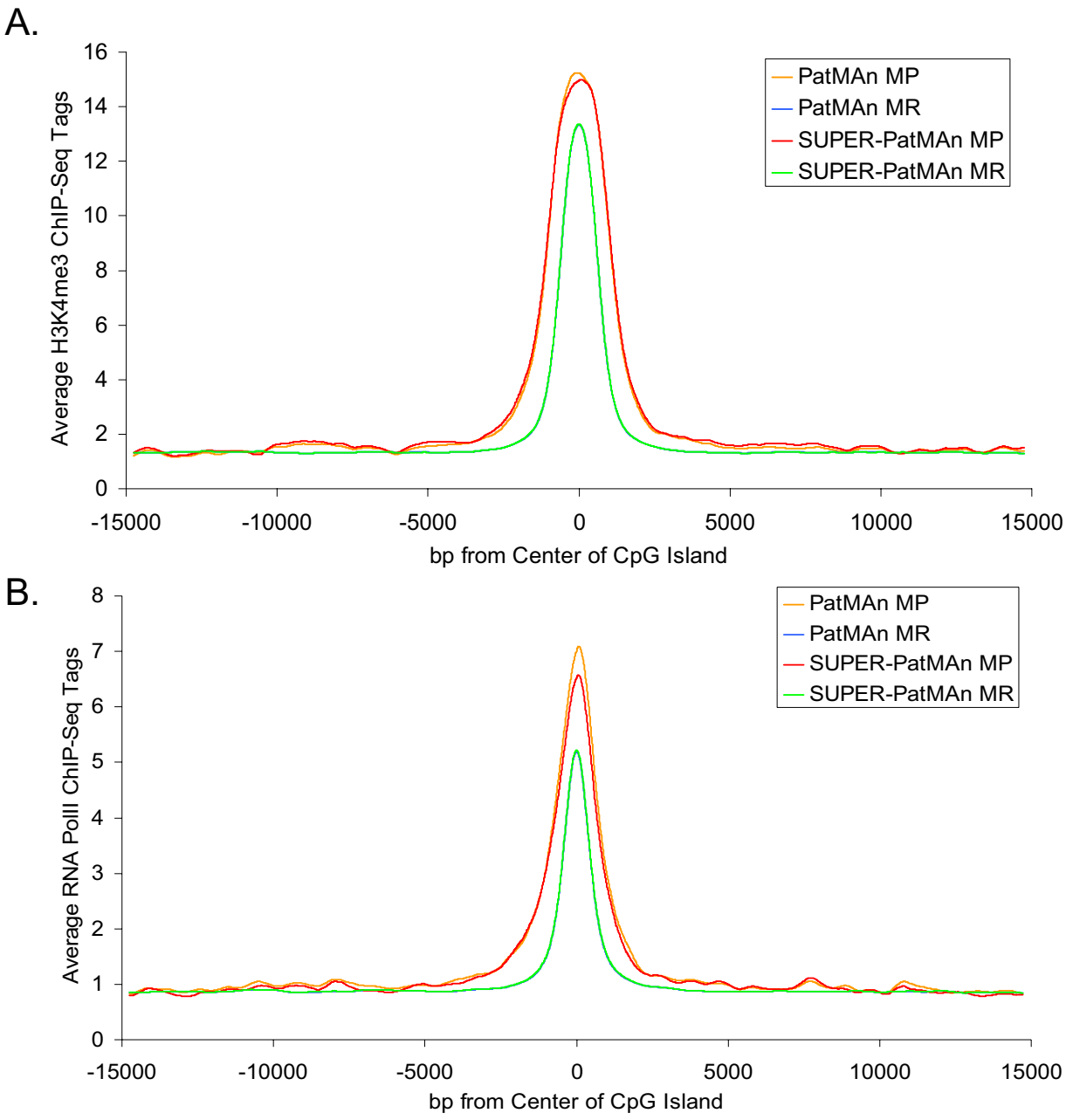


Supplementary Figure 1. CTCF binding does not correlate with CpG island methylation status. DNA fragments identified as methylation-prone or methylation-resistant by RLGS analysis were assessed for proximity to CTCF-enriched regions as defined by genome-wide ChIP-chip studies. Both methylation-prone and methylation-resistant fragments showed similar enrichment for CTCF (21% and 23%, respectively). The red fraction is enriched for CTCF, whereas the green fraction is not enriched for CTCF.



Supplementary Figure 2. Association of H3K27 histone modifications surrounding PatMAn and SUPER-PatMAn predictions. All human CpG islands were aligned by their centers and the average number of H3K27me3 or H3K27Ac ChIP-Seq tags was calculated extending out 10kb in each direction. H3K27me3 data is depicted by solid lines while H3K27Ac data is depicted by hashed lines.



Supplementary Figure 3. Correlation of H3K4me3 and PolII binding with PatMAn and SUPER-PatMAn predictions. CpG islands predicted by PatMAn or SUPER-PatMAn to be methylation-prone or methylation-resistant were assessed for proximity to **A**, H3K4me3- or **B**, PolII-enriched regions as defined by a genome-wide ChIP-seq study in CD4+ T cells (Barski et al, Cell, 823-837, 2007). CpG islands predicted to be methylation-prone and methylation-resistant by both classifiers showed similar enrichment for both H3K4me3 and PolII.

Supplementary Table 1. MSP Primers.

CpG Island	Methylation Status	Sense	Antisense
ADAMTS5	Unmethylated	GAGTTGTGAGGTTAGTGTTGTGT	ATAAATCCACACAAATCCTACACA
	Methylated	GTTGCGAGGTTAGTGTTGCGC	AATCCGCACGAATCCTACACG
AGPAT3	Unmethylated	TATAAGGTATTGGGTGTAGGAGGT	CACTATATCAACACTTAACCATAACA
	Methylated	AAGGTATCGGGCGTAGGAGGC	CTATATCGACACTTAACCGTAACG
ERG	Unmethylated	GTGAAAATGGTTGTGATATTAAGAT	CAAACCAAACCACAATACCCTCA
	Methylated	GAAAACGGTTGCGATATTAAGAC	AACCAAACCGCGATACCCTCG
HSF2BP	Unmethylated	AATTTTGGTAATTGAAAGGTAGTGTT	ATACCCTTCTCACTAAACACCAACCA
	Methylated	TTTGGTAATCGAAAGGTAGCGTC	CCCTTCTCGCTAAACGCCAACCG
ICOSLG	Unmethylated	GAGATTGTTTTGGGATAGGAGGT	ACACAACCAACCAAAAACCTAACA
	Methylated	GATCGTTTCGGGATAGGAGGC	GCAACCGACCAAAAACCTAACG
PKNOX1	Unmethylated	TGTGGGTTTTGATTGTTGTAGTT	CCTCCAAACCCAAACAACAACA
	Methylated	CGGGTTTCGATTGTTGTAGTC	CTCCAAACCCGAACGACAACG
SIM2	Unmethylated	GGGTTTTGTGGGTTTGGAGTAT	AACCACAACAACCCCCTCTAAACA
	Methylated	GGTTTCGCGGGTTTGGAGTAC	CCGCGACAACCCCCTCTAAACG
RUNX1	Unmethylated	ATTTAGTTTTTGGATTTTGGTTTT	AACACCCAAAAACAATCCCTACA
	Methylated	TAGTTTTCGGATTTCGGTTTC	CGCCCGAAAACAATCCCTACG
SIM2 Exon2	Unmethylated	GTATAGATGGTGGTTGTGGAGTT	AATCCCAACTCCTTAACAACACCA
	Methylated	ATAGATGGCGGTTGCGGAGTC	CCCAACTCCTTAACGACGCCG
CECR6	Unmethylated	GGTAGTAGGAGGTGTTGTTGTT	ACAACTCCCCAAACAACAACACA
	Methylated	GTAGTAGGAGGCGTCGTTGTC	GACTCCCCGAACAACAACACG
TIMP3	Unmethylated	AGTTTGGGTTGTAGTAGTTTTGTT	CTAACTACAACATAAAACTCAAACA
	Methylated	TTCGGGTTGTAGTAGTTTCGTC	AACTACAACGTAAAACTCGAACG
RBM9	Unmethylated	TTGATTGGTTGGGATTTTTTGATTT	AAATTCCCAAACTTCCCCAATCA
	Methylated	GATTGGTCGGGATTTTTCGATTC	ATTCCCGAACTTCCCCGATCG
MAFF	Unmethylated	TTAGGTAGAGAATTGTGGTAGTTTT	CCTCCACTCTAAACCACAAATCA
	Methylated	GGTAGAGAATCGCGGTAGTTTC	TCCGCTCTAAACCGCAAATCG
RBX1	Unmethylated	TTAAGAGGTGTGGTTATGTGTTTT	ACTTCAAAACACTTCTTACCCACA
	Methylated	AAGAGGCGTGGTTACGTGTTTC	TTCAAAACGCTTCTTACCCGCG
MAPK8IP2	Unmethylated	TTAATTAGTGTTTGGTAGTGAAGTT	TCACCTCATAACACACCCTACA
	Methylated	ATTAGCGTTCGGTAGTGAAGTC	ACCTCGTAACACGCCCTACG
SHANK3	Unmethylated	GAAGGTAGGTGTTGAGTTGAGTT	CTACTACAAATCCAAAATACCAACA
	Methylated	AGGTAGGCGTCGAGTTGAGTC	CTACAAATCCGAAATACCGACG
LIF	Unmethylated	GGAGTTTGTAAGTTGTTTGTTGTTT	TCCTCCTCACTCCAAACACTCA
	Methylated	AGTTTGTAAGTTGTTCGTCGTTC	CTCCTCGCTCCGAACACTCG
TBX1	Unmethylated	GGGGTTTTGGGTATGTTGGTATT	CAACAACTACAAAAAATACACCA
	Methylated	GGTTTCGGGTACGTTGGTATC	ACAACTACGAAAAATACGCCG
ADRBK2	Unmethylated	GAGAAGAGTAAGGTGATTTTGGTT	ACTAAAACAACAAAACCAACCCCA
	Methylated	GAAGAGTAAGGCGATTTCGGTC	TAAAACGACGAAACCGACCCCG
KCNJ6	Unmethylated	GAGTGGAGATGTTTGTGGTGAT	AACCTAAAACCAAAACAACCACA
	Methylated	AGTGGAGATGTTTGCGGCGAC	CCTAAAACCGAAACAACCGCG
MGC16635	Unmethylated	TGGTTTGGGAGATAGAGTTTGTT	CTACAAAACACAAAAAACAAACAACA
	Methylated	GTTCGGGAGATAGAGTTCGTC	ACAAAACGCGAAAAACGAACAACG
OLIG2	Unmethylated	GTTTAGGGTTGTAGTTGGAATTTT	ACCAAATCATCCTAATAAACCACA
	Methylated	TTAGGGTCGTAGTCGGAATTTC	CAAATCGTCCTAATAAACCGCG
PP2447	Unmethylated	GAAGTGATTGAGTGTTTGGGTTT	AAAATCAACCTAATCCATCCTCCA
	Methylated	AAGTGATTGAGCGTTCGGGTTC	ATCGACCTAATCCGTCCTCCG
GABPA	Unmethylated	GGAAGTGTTTTGGAGATAGTTTGT	CCTAACAAACAAAACACTAACTCA
	Methylated	AAGCGTTTCGGAGATAGTTTGC	CTAACGAACAAAACGCTAACTCG
TIAM1	Unmethylated	GTTGTAGAGTGATTATGGGTGTAT	CAATCCCACCAATACCAAACCA
	Methylated	TGTAGAGCGATTATGGGCGTAC	AATCCCACCGATACCGAACCG
ITSN1	Unmethylated	TTTGGATTATGGGTGGTTGTAGT	CCAACCTCCCAATACAAATCCA

	Methylated	TGGATTACGGGCGGTTGTAGC	CGACCTCCCAATACGAATCCG
CBR3	Unmethylated	TTTTAGGTGGTTTGAAGTTTGGTTT	AAAAACACAAACTCAAACCCTCCA
	Methylated	TAGGTGGTTCGAAGTTCGGTTC	AACGCGAACTCAAACCCTCCG
TTC3	Unmethylated	TTTTGGGTGGGAGTTAGTGAGT	ACACATCCAAAAACCCAACAACA
	Methylated	TCGGGTGGGAGTTAGCGAGC	ACATCCGAAAACCCGACAACG
ETS2	Unmethylated	TTAGAGATTGATGAGTGTGGTGTT	CCCTACCACTACAAACAAAACCA
	Methylated	GAGATTGACGAGTGCGGTGTC	CTACCGCTACGAACAAAACCG
BACE2	Unmethylated	GGAAGAGGTGTGGTTTGAGTTT	CAACCTAACCAATCCCATCCCA
	Methylated	GAAGAGGCGCGGTTTGAGTTC	ACCTAACCGATCCCGTCCCG
RIPK4	Unmethylated	TTTTGGGTGGTTAGGTGTAGTGT	CCTCATCAACCTATACTCCAACA
	Methylated	TGGGCGGTTAGGTGTAGCGC	TCATCGACCTATACTCCGACG
U2AF1	Unmethylated	GTTAGGTGAGGTGTTGTTTGTGT	TCAAACTAAACACCCCCCACCA
	Methylated	TAGGCGAGGTGTTGTTTGCGC	GAACTAAACGCCCCCCACCG
C21orf33	Unmethylated	GAGGGGTTGTTTTGTGGGAGTT	CCATCAAACACCTCCACAAACA
	Methylated	GGGGTCGTTTCGTGGGAGTC	CATCGAACGCCTCCACAAACG
PFKL	Unmethylated	TTATTGGGGTTTTGGTGTTGGT	AAAAATCCTACACCCTCAACCCA
	Methylated	ATCGGGGTTTCGGCGTTGGC	AATCCTACGCCCTCGACCCG
POFUT2	Unmethylated	GGAGGTTGTGGTTGTGGTTTGT	CAAACTCTCATACACAACTCCCA
	Methylated	AGGTCGTGGTTGTGGTTCGC	AACTCTCATACGCGACTCCCG
DGCR6	Unmethylated	TAGTTATTATGGAGGGATGGGGT	CCAACTCACATCATCCCAACCA
	Methylated	TTATTACGGAGGGACGGGGC	AACTCACGTCATCCCGACCG
PPM1F	Unmethylated	GTGTTTTGTAAGTTGTTGTTGGTT	AAAAAACCACAATCACCATCCACA
	Methylated	GTTTCGTAAGTTGTTGTCGGTC	AAACCGCAATCACCGTCCACG
MIF	Unmethylated	AAGTTAGGTATGTAGTTTAGTGGT	CCACTTCAAACCCAAACCACCA
	Methylated	GTTAGGTACGTAGTTTAGCGGC	ACTTCGAACCCGAACCACCG
TPST2	Unmethylated	TTAGGGTTATTTATTGTGGTGAGAT	AACAAACCTCCAAAAAACTTCCCA
	Methylated	GGGTTATTTATCGTGGCGAGAC	GAACCTCCGAAAAACTTCCCG
OSBP2	Unmethylated	GGGAGTTTGTATGGGTGTTTGT	AAACAACCTCCAATCAACAAAACA
	Methylated	GGAGTTTGTATGGGCGTTCGC	ACAACCTCCAATCGACGAAACG
LARGE	Unmethylated	GAGTTGGGTGGTTGTTGTAGTT	CTACAACTACTAAACAAATCCAACA
	Methylated	AGTTGGGCGGTCGTTGTAGTC	ACAACTACTAAACGAATCCGACG
CBX7	Unmethylated	TGGTTTGGTTATTGGTTGGGGT	TACAACTCAAAAAACTACACCTCA
	Methylated	GTTCGGTTATCGGTTGGGGC	CAACTCGAAAAACTACGCCTCG
A4GALT	Unmethylated	GGGTTTGGTGGGAGGTAGTATT	CACTCCCTACCTATTAACCAACA
	Methylated	GTTCGGCGGGAGGTAGTATC	CTCCCTACCTATTAACCGACG
CELSR1	Unmethylated	GTTTTTGTATTTATTTGGTGAGGTT	CCTAAAACCACCTAAAACCACCA
	Methylated	TTTCGTATTTATTCGGCGAGGTC	TAAAACCGCCTAAAACCGCCG

Supplementary Table 2. CpG islands from the HG17 build of the human genome predicted to be Predicted MP by PatMAn and/or SUPER-PatMAn.

HG17 CpGi Coordinates	PatMAn	SUPER-PatMAn
chr1:100528797-100530873	Predicted MP	Predicted MP
chr1:10636283-10636985	Predicted MP	Predicted MP
chr1:10687828-10689992	Predicted MP	Predicted MP
chr1:107394371-107396745	Predicted MP	Predicted MP
chr1:10787809-10790035	Predicted MP	Predicted MP
chr1:10790350-10791562	Predicted MP	Predicted MP
chr1:109307459-109308489	Predicted MP	Predicted MP
chr1:109327802-109328704	Predicted MP	Predicted MP
chr1:110464156-110467124	Predicted MP	Predicted MP
chr1:1109039-1109588	Predicted MP	Predicted MP
chr1:112243282-112245943	Predicted MP	Predicted MP
chr1:112762922-112764722	Predicted MP	Predicted MP
chr1:116627001-116629350	Predicted MP	Predicted MR
chr1:11730066-11730716	Predicted MP	Predicted MP
chr1:119260991-119263553	Predicted MR	Predicted MP
chr1:120547664-120551733	Predicted MP	Predicted MP
chr1:12896472-12897088	Predicted MP	Predicted MP
chr1:1323583-1326968	Predicted MP	Predicted MP
chr1:1329458-1331289	Predicted MP	Predicted MR
chr1:142564304-142565342	Predicted MP	Predicted MP
chr1:142962020-142963478	Predicted MP	Predicted MR
chr1:146192045-146193244	Predicted MP	Predicted MR
chr1:146388649-146390964	Predicted MP	Predicted MR
chr1:146576984-146578182	Predicted MP	Predicted MR
chr1:147636475-147637080	Predicted MP	Predicted MP
chr1:148821810-148823620	Predicted MP	Predicted MR
chr1:150367780-150368747	Predicted MP	Predicted MP
chr1:150463767-150466058	Predicted MP	Predicted MP
chr1:150707391-150709374	Predicted MP	Predicted MP
chr1:151190375-151191689	Predicted MP	Predicted MP
chr1:151286898-151289200	Predicted MP	Predicted MP
chr1:151746834-151748137	Predicted MP	Predicted MR
chr1:151976393-151978507	Predicted MP	Predicted MP
chr1:153406657-153408944	Predicted MP	Predicted MP
chr1:153828007-153829595	Predicted MP	Predicted MR
chr1:157811829-157812559	Predicted MP	Predicted MP
chr1:158222559-158227297	Predicted MP	Predicted MP
chr1:158229113-158234677	Predicted MP	Predicted MP
chr1:158236491-158242282	Predicted MP	Predicted MP
chr1:158243904-158249468	Predicted MP	Predicted MP
chr1:158251284-158255850	Predicted MP	Predicted MP
chr1:15906142-15909632	Predicted MR	Predicted MP
chr1:1594492-1596277	Predicted MP	Predicted MR
chr1:168541593-168543089	Predicted MP	Predicted MP
chr1:170313507-170314009	Predicted MP	Predicted MP
chr1:170567997-170569944	Predicted MP	Predicted MP
chr1:172907043-172908711	Predicted MP	Predicted MP
chr1:173882274-173882905	Predicted MP	Predicted MR

chr1:177332445-177333760	Predicted MP	Predicted MP
chr1:180171673-180174270	Predicted MP	Predicted MP
chr1:185926240-185926820	Predicted MP	Predicted MP
chr1:18712135-18713646	Predicted MR	Predicted MP
chr1:194612175-194614150	Predicted MR	Predicted MP
chr1:199507502-199509658	Predicted MP	Predicted MP
chr1:201216835-201217860	Predicted MP	Predicted MP
chr1:201385561-201386887	Predicted MR	Predicted MP
chr1:202043970-202045604	Predicted MP	Predicted MR
chr1:202156374-202158461	Predicted MP	Predicted MR
chr1:20555603-20558607	Predicted MP	Predicted MP
chr1:208236865-208238206	Predicted MP	Predicted MR
chr1:210548978-210549857	Predicted MP	Predicted MP
chr1:211112249-211114077	Predicted MP	Predicted MP
chr1:2152098-2153916	Predicted MP	Predicted MP
chr1:217438460-217439575	Predicted MP	Predicted MP
chr1:218303615-218305499	Predicted MP	Predicted MP
chr1:219908482-219910637	Predicted MP	Predicted MR
chr1:220927911-220929839	Predicted MP	Predicted MR
chr1:222109889-222110482	Predicted MP	Predicted MP
chr1:224440956-224443274	Predicted MP	Predicted MP
chr1:224900249-224901742	Predicted MP	Predicted MP
chr1:225049129-225091154	Predicted MP	Predicted MP
chr1:227481404-227483490	Predicted MP	Predicted MP
chr1:227603149-227606759	Predicted MP	Predicted MP
chr1:231815992-231818487	Predicted MP	Predicted MP
chr1:231992921-231995122	Predicted MP	Predicted MP
chr1:232630525-232632948	Predicted MR	Predicted MP
chr1:23288428-23289749	Predicted MP	Predicted MR
chr1:233530926-233532985	Predicted MP	Predicted MP
chr1:23415156-23416970	Predicted MP	Predicted MP
chr1:23575189-23576217	Predicted MP	Predicted MP
chr1:236696863-236697666	Predicted MP	Predicted MP
chr1:23759987-23761240	Predicted MP	Predicted MP
chr1:23871591-23873217	Predicted MP	Predicted MP
chr1:23924394-23925183	Predicted MP	Predicted MP
chr1:240536833-240539349	Predicted MP	Predicted MP
chr1:240940211-240941879	Predicted MP	Predicted MP
chr1:243779518-243780314	Predicted MP	Predicted MR
chr1:245165666-245166411	Predicted MP	Predicted MP
chr1:25000409-25004720	Predicted MP	Predicted MP
chr1:26705625-26708325	Predicted MP	Predicted MR
chr1:27332315-27333449	Predicted MP	Predicted MR
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chr6:107066409-107067891	Predicted MP	Predicted MP
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chr6:114397775-114399719	Predicted MP	Predicted MP
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chr6:1333895-1336598	Predicted MP	Predicted MR
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chr6:137154119-137156349	Predicted MR	Predicted MP
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chr7:148593994-148596100	Predicted MP	Predicted MR
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chrX:72565697-72566744	Predicted MP	Predicted MP
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chrX:9562999-9565140	Predicted MP	Predicted MR
chrX:99467628-99472901	Predicted MP	Predicted MP
chrY:12514030-12514966	Predicted MP	Predicted MP
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chrY:272350-276708	Predicted MP	Predicted MP
chrY:368142-369130	Predicted MP	Predicted MP
chrY:560242-563412	Predicted MP	Predicted MP

Supplementary Table 3. Partial list of genes predicted by SUPER-PatMAn to be methylation-prone with evidence for cancer-associated hypermethylation.

Gene	PubMed ID
ADAMTS9	16799631
ALDH1A3	16367923
ARF4	16900213
BAHRHL2	18162535
C9orf64	17303177
CBLN2	18162535
CBLN4	18162535
CCND2	7529333
CDC4	17909001
CDH11	18162535
CDKN1B	11042700
CDKN2C	16207477
CDX2	15706431
CFTR	15526362
CLDN7	12673207
COMP	16444255
CSMD1	16153303
CTNNA1	17159988
DAB2IP	12446720
DACT1	15580286
DCC	11461076
DSC2	16168112
DVL1	15256063
EFEMP2	16778180
EGR2	14596916
EGR3	15342380
EMX2	15342380
EYA4	15824152
FGFR2	17456767
FLJ45983	16575877
FOXA2	15205324
FOXD2	18162535
FRAT1	15251184
GATA4	14612389

Gene	PubMed ID
GATA6	18162535
GBX2	16778180
GPR7	17437806
GRIN2B	18158559
GRM7	15059895
HAND1	12438262
HIC1	7585125
HOXA7	17369352
HRK	14695142
IGFBP7	17334979
ING1	15677627
JUN	12506033
KCNK15	16707430
KLF4	14724568
LAMA3	14695139
LHX1	12839967
LHX2	16912168
LHX6	16732332
LRP15	15840217
MAD1L1	18162535
MEIS2	18162535
MINT1	11839573
MXI1	15574775
MYOD1	2385586
NFATC1	18156209
NKX6.1	17363581
NKX6.2	18162535
NR2E1	18162535
NR2F2	18162535
NTN1	17967459
NTSR1	15467763
OTX2	18162535
PARK2	16287063

Gene	PubMed ID
PAX5	12907641
PAX7	16912168
PMP24	14712230
POU3F3	16900213
PROX1	12874782
PTCH	17295047
RFX1	15334059
RUNX3	11955451
SALL3	18094410
SALL4	17546590
SERPINH1	15231663
SHH	18162535
SHOX	18162535
SIM2	10655057
SIX2	16912168
SOCS1	11326271
SOCS2	15361843
SOX9	18087279
SYK	11454707
TBX3	16367923
TCF2	16479257
THSD2	10359534
TIMP3	9916800
TITF1	17504987
TLL1	15467763
TLX2	16778180
TOP1	8938793
TPM1	12065096
WNT2	18162535
WNT9A	16707430
ZIC1	17369352
ZIC4	18162535
ZIC5	18162535

Supplementary Table 4. WNT, Hedgehog, Notch, and TGF-beta pathway genes predicted to be methylation-prone by SUPER-PatMAn with evidence of cancer-associated hypermethylation.

Gene	PubMed ID
CCND2	14506731
DVL1	15256063
FRAT1	15251184
WNT2	16444255
WNT9A	16707430
WNT10B	17761539
WNT11	16318277
PTCH	17295047
COMP	16444255