

Supplemental Data

Divergent Whole-Genome Methylation Maps of Human and Chimpanzee Brains Reveal

Epigenetic Basis of Human Regulatory Evolution

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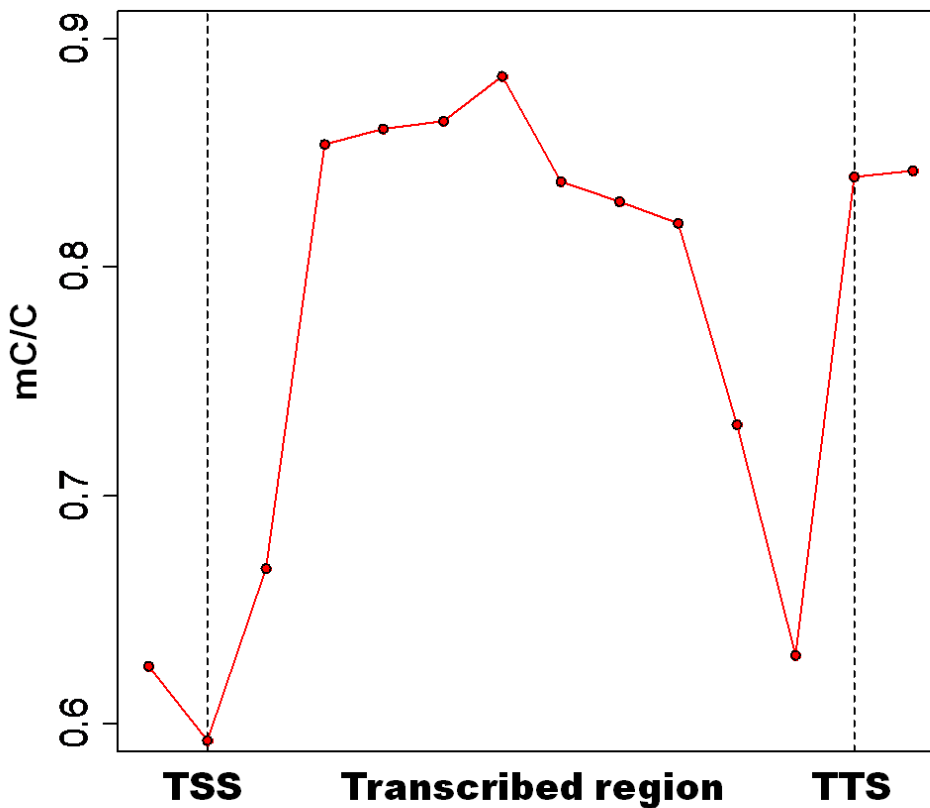


Figure S1. Variation of Methylation Levels in Human Transcription Units

CG methylation profiles along the transcribed region plus 2kb upstream the transcription start site (TSS) and 2kb downstream the transcription end site (TTS). Each point indicates the mean CG methylation level for each equal size bin in the transcribed region or the 1kb interval in the untranslated region.

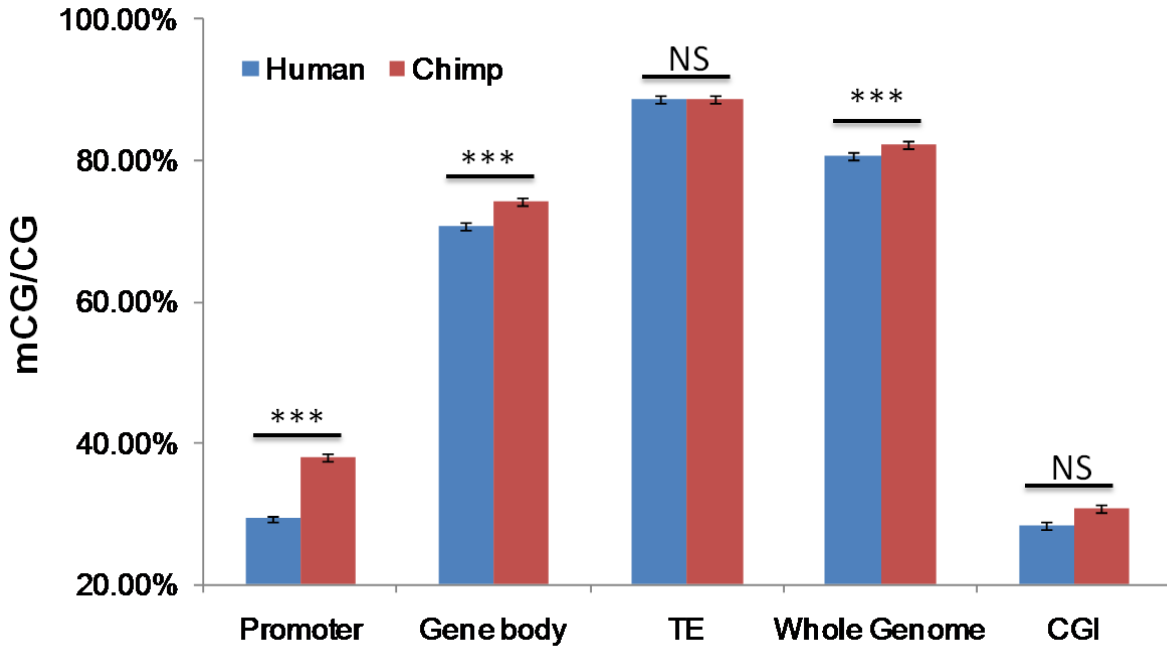


Figure S2. Differences in Fractional Methylation Levels between Human and Chimpanzee Brains

The mean fractional methylation levels (\pm S.E.) of different genomic regions. *** $P < 10^{-15}$, NS: Not Significant, Wilcoxon test. Promoters are the most differentially methylated; human promoters on average exhibit 23% lower methylation relative to chimpanzee promoters (mean mCG/CG levels are 0.293 and 0.381 for human and chimpanzee promoters, respectively. The difference is $(0.381 - 0.293) / 0.381 = 23\%$). Interestingly, TEs still exhibit similar, high levels of DNA methylation, which is in line with a strong silencing effect.

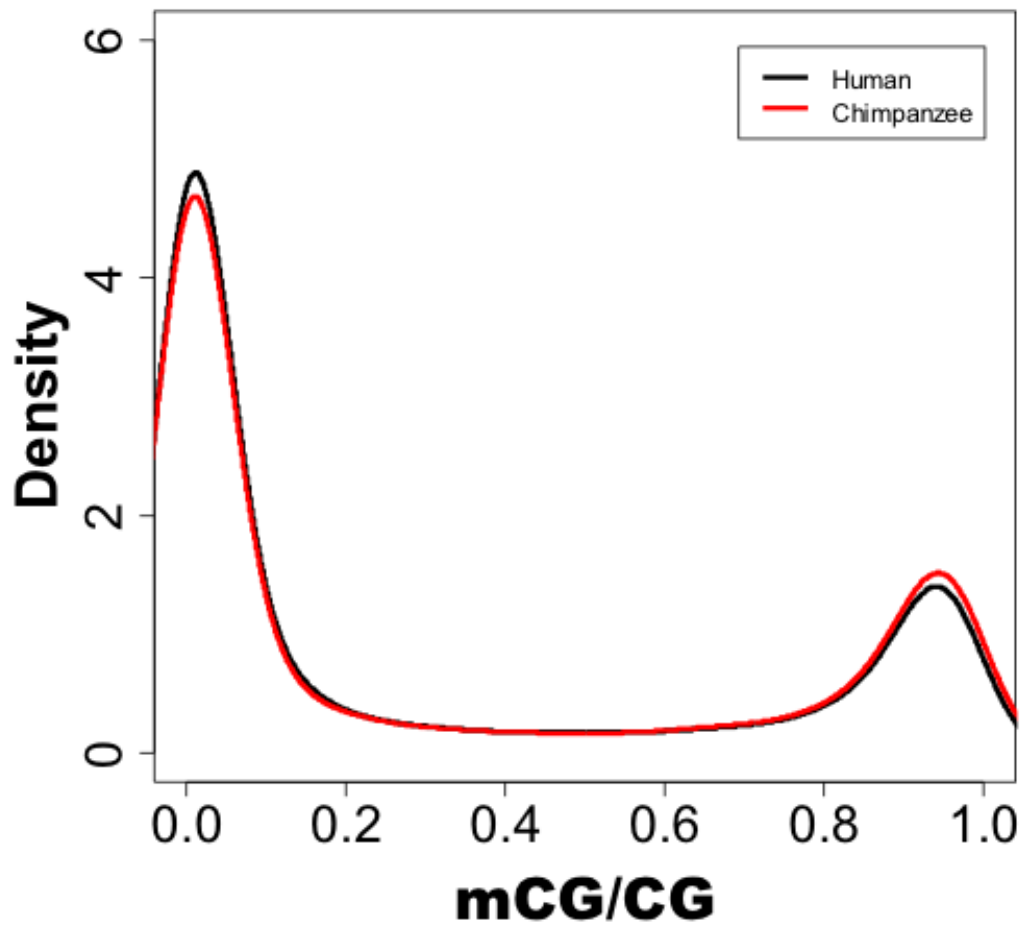


Figure S3. Density Distributions of Human and Chimpanzee CpG Island Fractional Methylation Levels

CpG islands exhibit no evidence of differential methylation between human and chimpanzee genomes (Wilcoxon test, $P = 0.2327$).

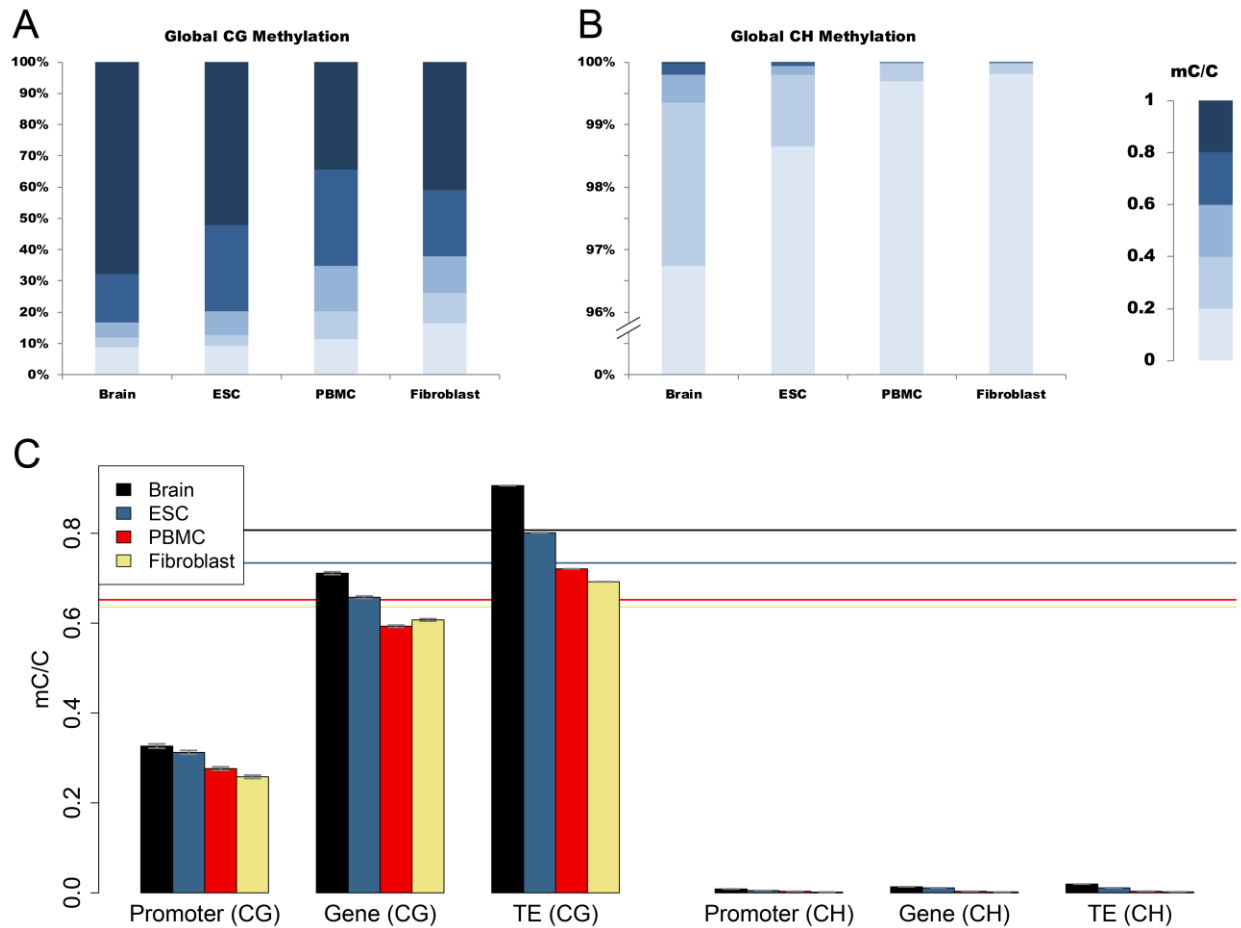


Figure S4. Differences in DNA Methylation Levels among Human Tissues and Genomic Features, after Removing Duplicate Reads from Brain Sample

(A) Proportional representation of genome-wide DNA methylation levels for individual CG dinucleotides in human prefrontal cortex (brain), embryonic stem cells (ESC), neonatal fibroblasts (fibroblast), and peripheral blood mononuclear cells (PBMC).

(B) Same analyses as in (A), but for CH dinucleotide context (H = A, T, or C).

(C) Mean methylation levels in each tissue for gene promoters (CG context N = 18,368, CH context N = 18,566), gene bodies (CG context N = 18,454, CH context N = 18,640), and transposable elements (CG context N = 1,763,067, CH context N = 2,919,957). Horizontal lines indicate global means of methylation levels for individual CG sites. Error bars, 95% confidence intervals of the mean.

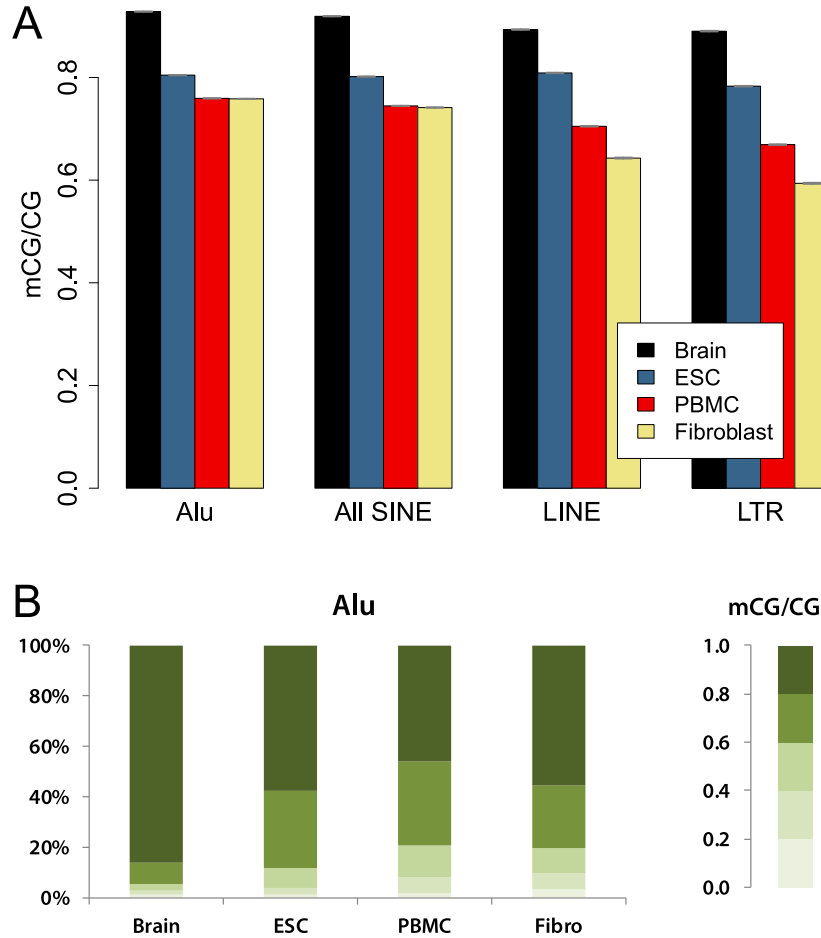


Figure S5. Differences in DNA Methylation Levels for Transposable Element Classes among Human Tissues

(A) Mean CG methylation levels in human prefrontal cortex (brain), embryonic stem cells (ESC), neonatal fibroblasts (fibroblast), and peripheral blood mononuclear cells (PBMC) for the following classes of transposable elements as identified by RepeatMasker: Alu elements (N = 881,311), all short interspersed elements including Alu (All SINE; N = 1,043,521), long interspersed elements (LINE; N = 370,983), and long terminal repeats (LTR; N = 291,925).

(B) Proportional representation of mean CG methylation levels for each Alu element.

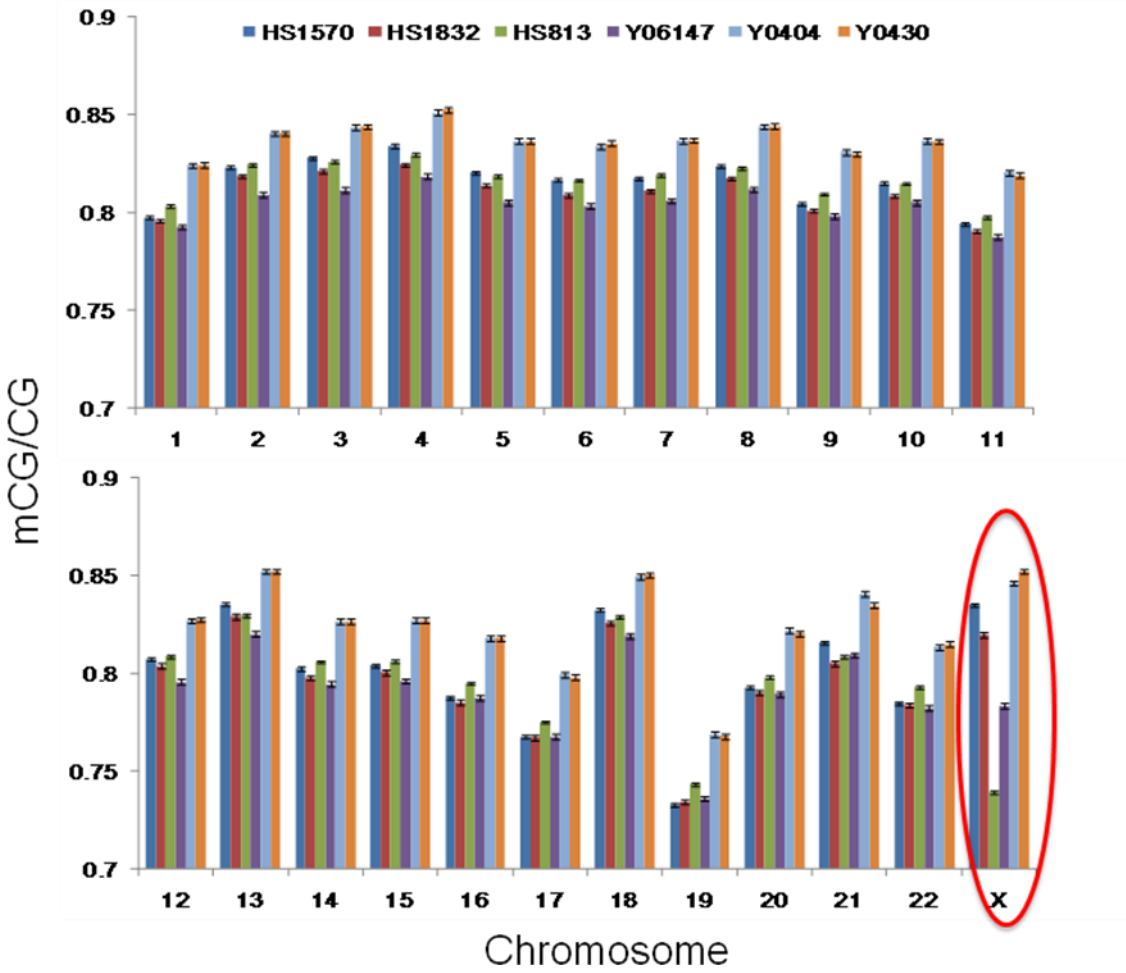


Figure S6. Chromosome-wide Variation of DNA Methylation in Human and Chimpanzee Individuals

The X chromosome is notably hypomethylated in the female sample (Hs813).

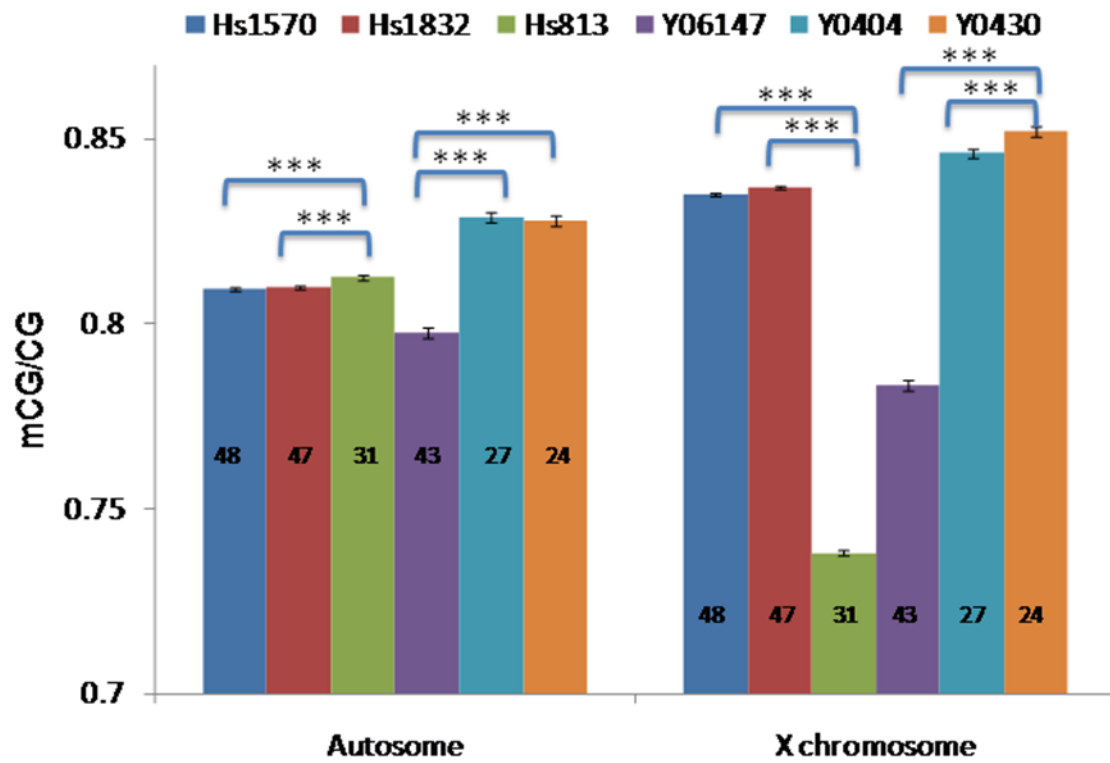


Figure S7. DNA Methylation Level (\pm S.E.) in Autosomes and the X Chromosomes between Human and Chimpanzee Samples

*** $P < 10^{-15}$, Wilcoxon test. The age of each individual are shown within each bar plot. The X chromosome is notably hypomethylated in the female individual (Hs813).

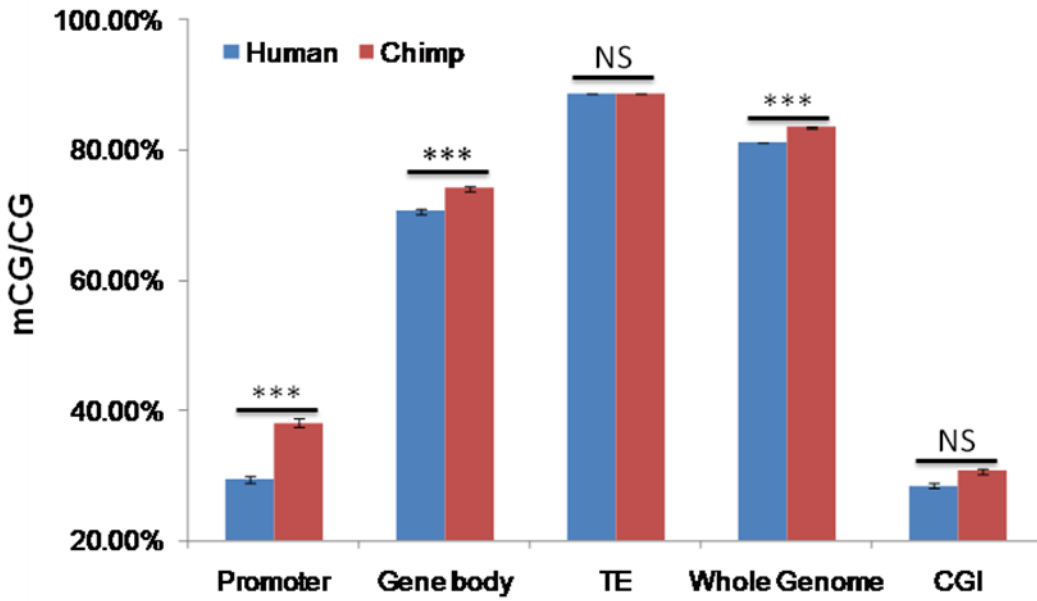


Figure S8. Differences in Fractional Methylation Levels between Human and Chimpanzee Brains, When Only Autosomal Data Are Used

The mean fractional methylation levels (\pm S.E.) of different genomic regions. *** $P < 10^{-15}$, NS: Not Significant.

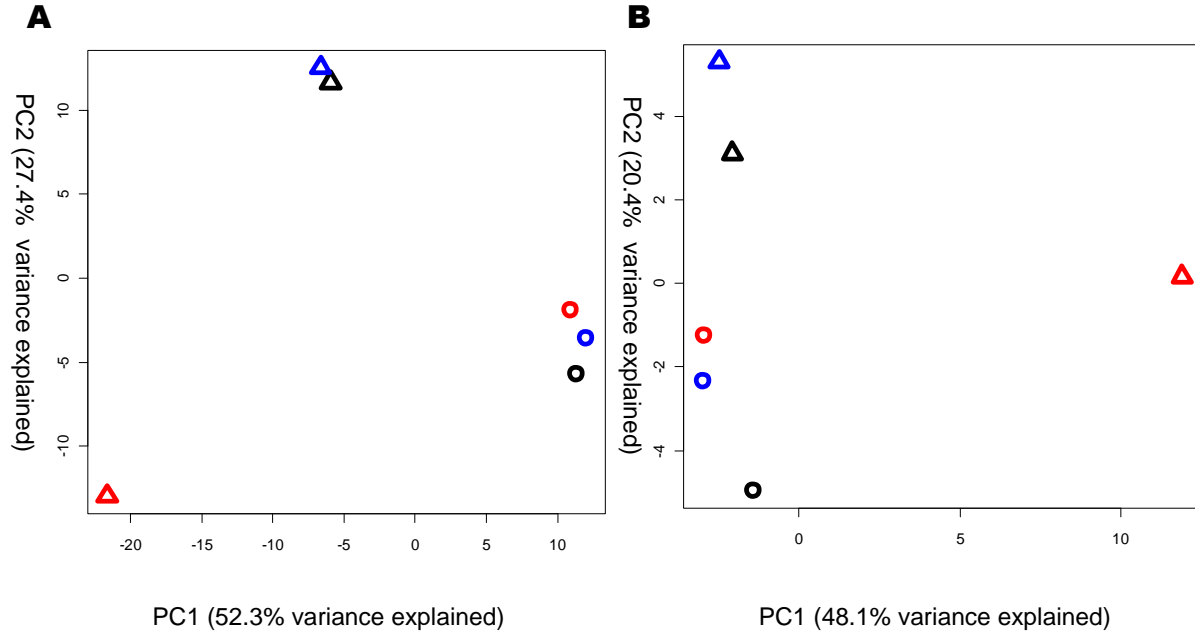


Figure S9. Variation of Genomic DNA Methylation in the Human Brains (n = 3) and in the Chimpanzee Brains (n = 3), after Removing Orthologs in X Chromosome

Principal component analysis of six methylation profiles, at both of the promoter (A) and gene body (B). PC1 and PC2, together with their explained variation, are plotted on the x-axis and y-axis, respectively. The first principal component, which explains 52.3% and 48.1% of variation in promoter and gene body respectively, separates two human samples from the third one. The second principal component, explaining 27.4% and 20.4% of total variation in promoter and gene body respectively, distinguishes samples from human and chimpanzees.

Table S1. Descriptions of Six Individuals Used for Methylation Analyses

Species	ID	Age	Sex	Cause of Death	Numbers of Total Reads ($\times 10^6$)
Human	Hs1570	48	Male	Accident	354.9
Human	Hs1832	47	Male	Cardiovascular disease	327.1
Human	Hs813	31	Female	Accident	343.1
Chimpanzee	Y06147	43	Male	Congestive heart failure	309.0
Chimpanzee	Y0404	27	Male	Cardiac fibrosis	391.4
Chimpanzee	Y0430	24	Male	Myocardial fibrosis	331.2

Table S2. Human and Chimpanzee Samples Used for Expression Analyses

Sample	Age	Sex	PMI	RIN	Identifier	Cause of Death
<i>Homo sapiens</i>						
Hs_FP_1	31	F	14	7.9	813	Accident
Hs_FP_2	40	M	7	7.2	1903	Cardiovascular disease
Hs_FP_3	30	M	12	6.8	1029	Accident
Hs_FP_4	20	F	4	6.8	4548	Injuries from motor vehicle accident
Hs_FP_5	45	M	6	7.2	4598	Dilated cardiomyopathy
Hs_FP_6	42	M	15	6.8	1134	Cardiovascular disease
<i>Pan troglodytes</i>						
Pt_FP_1	18	M	3	7.6	Y07.147	Cardiac fibrosis
Pt_FP_2	27	M	0.5	5.1	Y04.04	Cardiac fibrosis
Pt_FP_3	43	M	2.5	4.3	Y06.147	Myocardial fibrosis
Pt_FP_4	21	M	13	4.5	Y03.09	Liver failure
Pt_FP_5	44	F	0.5	3.1	Y06.108	Atherosclerosis
Pt_FP_6	28	M	3	4.1	Y05.12	Cardiac fibrosis

PMI=post mortem interval in hours; Age is in years

RIN=RNA integrity number

Table S3. Comparison of CpG Methylation from Enard et al [8]

Gene	Human Coordinate	Human mCG/CG (Total # of reads)	Chimp coordinate	Chimpanzee mCG/CG (Total # of Reads)
CTLA4_4	chr2:204735456	100% (39)	chr2b:209400249	100% (10)
UBC_2	chr17:16284399	0% (100)	chr17random:2377926	0% (13)
UBC_3	chr17:16284414	0% (92)	chr17random:2378140	0% (9)
EGFR_4	chr2:73520852	0% (10)	chr2a:74879569	0% (4)
MYCL1_2	chr1:40367966	0% (30)	chr1:40541066	0% (5)
LTA_1	chr6:31540014	100% (8)	chr6:32134113	100% (12)
GP1BB_2	chr22:19710890	100% (27)	chr22:18179194	100% (13)
GP1BB_3	chr22:19710984	100% (7)	chr22:18179288	100% (7)
CDC25A_1	chr3:48229881	0% (5)	chr3:49296979	0% (N/A)
POMC_3	chr2:25391523	0% (8)	chr2a:25701886	0% (11)
EGR4_4	chr2:73520819	0% (14)	chr2a:74879569	0% (16)
SLC25A4_1	chr4:186064167	0% (2)	chr4:189828250	0% (5)
SLC25A4_3	chr4:186064191	0% (5)	chr4:189828276	0% (N/A)
CD63_4	chr12:56122912	0% (7)	chr12:33919706	0% (N/A)

All the individual CpG site in the following table are reported to be significantly differentially methylated between human and chimpanzee according to Enard et al [8]. The mCG/CG values are calculated based on all the 3 individuals in human or chimpanzee from our data.

Table S4. 468 Genes for which the Human Promoters Exhibit Hypomethylation compared to the Chimpanzee Promoters

Gene	Human_FM	Chimp_FM	Gene	Human_FM	Chimp_FM
NM_000561	0.123955	0.957179	NM_153006	0.198726	0.9512
NM_001408	0.147459	0.943429	NM_173079	0.109816	0.947909
NM_001688	0.055405	0.8015	NM_174887	0.016233	0.864818
NM_001779	0.108063	0.924409	NM_176096	0.036585	0.861733
NM_002506	0.181879	0.904218	NM_176863	0.051545	0.804917
NM_002524	0.164	0.9175	NM_177550	0.148594	0.833333
NM_002884	0.084507	0.804	NM_178517	0.006975	0.957684
NM_003051	0.012245	0.92519	NM_183377	0.010371	0.905083
NM_003594	0.045553	0.969963	NM_001071	0.170956	0.914971
NM_003846	0.140669	0.870231	NM_001279	0.132136	0.835417
NM_004978	0.08493	0.824231	NM_002828	0.071892	0.957596
NM_005399	0.073585	0.882952	NM_002845	0.009803	0.9266
NM_005725	0.064017	0.990786	NM_003409	0.011448	0.888684
NM_005872	0.158102	0.956091	NM_003799	0.014978	0.997079
NM_006090	0.021891	0.875	NM_005433	0.048833	0.940355
NM_006099	0.112411	0.830306	NM_006101	0.016932	0.992071
NM_006135	0.022423	0.895591	NM_006471	0.095408	0.889545
NM_006402	0.13143	0.93342	NM_006796	0.016441	0.802074
NM_006468	0.005824	0.886	NM_014214	0.042101	0.864765
NM_006492	0.144102	0.873344	NM_020412	0.003628	0.927714
NM_006608	0.097479	0.961556	NM_020648	0.150178	0.944421
NM_006699	0.005938	0.8148	NM_023075	0.05123	0.962938
NM_006784	0.029517	0.95625	NM_024899	0	0.97
NM_007204	0.077615	0.970727	NM_031216	0.015949	0.953727
NM_014455	0.05417	1	NM_032048	0.11427	0.92232
NM_015013	0.031145	1	NM_130386	0.158992	0.93084
NM_015836	0.169321	0.960526	NM_145287	0.189	0.811833
NM_015906	0.057453	1	NM_152352	0.017051	0.973625
NM_016361	0.15604	0.991308	NM_153000	0.154793	0.955188
NM_017686	0.001477	0.819586	NM_170695	0.006333	0.898706
NM_017709	0.08558	0.932353	NM_173464	0.189265	0.886885
NM_017744	0.00591	0.888889	NM_002850	0.174781	0.826194
NM_018704	0.103744	0.965909	NM_014475	0.119737	1
NM_022836	0.028069	0.859818	NM_020951	0.013554	0.85
NM_024102	0.068122	0.888933	NM_021185	0.188991	0.853333
NM_024494	0.086665	0.89308	NM_032838	0.083889	0.872727

NM_025073	0.192275	1		NM_032885	0.045273	0.867667
NM_025188	0.090398	0.992		NM_133466	0.119688	0.971278
NM_138959	0.155515	1		NM_002381	0.139024	1
NM_152696	0.05511	0.953651		NM_017933	0.179681	0.838714
NM_172212	0.109659	0.945538		NM_025029	0.07486	0.874127
NM_178454	0.012432	1		NM_002969	0.129569	1
NM_181643	0.057279	0.901125		NM_000335	0.148852	0.997
NM_005437	0.16426	0.892195		NM_130384	0.08023	0.866667
NM_033338	0.103467	0.939455		NM_000222	0.093491	0.907971
NM_001923	0.140068	0.818872		NM_000232	0.10655	0.920389
NM_003377	0.168358	1		NM_000807	0.073957	0.922652
NM_015533	0.004303	0.959259		NM_000812	0.145	0.98268
NM_017515	0.177496	0.977273		NM_000938	0.018542	0.853667
NM_000075	0.046628	0.905318		NM_001511	0.17388	0.981579
NM_000376	0.081042	0.859864		NM_001553	0.028242	0.919107
NM_000456	0.060129	0.979545		NM_001812	0.016197	1
NM_001659	0.186029	0.806		NM_002089	0.170761	0.907611
NM_001714	0.117212	0.97875		NM_002253	0.02521	0.861
NM_002135	0.117227	0.912033		NM_002703	0.003588	1
NM_002178	0.187515	0.83576		NM_002993	0.115973	0.960586
NM_002206	0.02778	0.868357		NM_002994	0.094109	0.958045
NM_002223	0.073809	0.976167		NM_003215	0.128128	0.960731
NM_002300	0.123619	0.97355		NM_003943	0.105404	0.886455
NM_002733	0.076185	0.944273		NM_004354	0.030986	0.838935
NM_002822	0.044908	0.949027		NM_004439	0.019843	0.849045
NM_002868	0.000283	0.823357		NM_004464	0.020727	0.966667
NM_002907	0.039953	0.895737		NM_004885	0.094266	0.80148
NM_003034	0.005516	0.974556		NM_004898	0.021768	0.927704
NM_003394	0.161438	0.855263		NM_005506	0.040905	0.995304
NM_003483	0.023468	0.986743		NM_005612	0.169511	0.964439
NM_003622	0.17756	0.970378		NM_006206	0.087055	0.915225
NM_003920	0.130366	0.956522		NM_006452	0.036481	0.90075
NM_004264	0.063833	0.943714		NM_006665	0.11118	0.85425
NM_004302	0.033241	0.944625		NM_006681	0.05172	0.983333
NM_004719	0.001233	0.9562		NM_006835	0.172965	0.824357
NM_004858	0.10884	0.888273		NM_006947	0.097042	0.890467
NM_005164	0.118373	0.899933		NM_012110	0.010053	0.933353
NM_005171	0.086736	0.9389		NM_012297	0.064029	0.859381
NM_005176	0.025229	0.857132		NM_014243	0.160694	0.978737
NM_005371	0.059494	1		NM_014933	0.055868	0.974

NM_005419	0.133356	0.945		NM_014991	0.008014	1
NM_005748	0.135917	0.872848		NM_015115	0.026846	0.970222
NM_005811	0.040935	0.9625		NM_015436	0.070511	0.947867
NM_005981	0.138795	0.923885		NM_015697	0.088079	0.9295
NM_006231	0.004118	0.806094		NM_016067	0.106848	0.851615
NM_006601	0.109889	0.970588		NM_017426	0.039159	0.909619
NM_006928	0.04707	0.928968		NM_017845	0.109632	0.938611
NM_006940	0.132476	0.968842		NM_018227	0.071931	1
NM_007211	0.007212	0.8917		NM_018243	0.042377	0.970258
NM_012117	0.000153	0.840679		NM_018261	0.163636	1
NM_013254	0.010564	0.855296		NM_018475	0.16746	0.938816
NM_013277	0.164617	0.912944		NM_020236	0.077043	1
NM_014182	0.011899	0.847		NM_020368	0.159378	0.9935
NM_014191	0.101948	0.986426		NM_020453	0.135367	0.8901
NM_014254	0.042683	0.994792		NM_021114	0.180101	0.986842
NM_014255	0.078259	0.942857		NM_022832	0.064167	1
NM_014319	0.112356	1		NM_024592	0.055655	0.923083
NM_014764	0.142341	0.901909		NM_024672	0.003899	0.952
NM_015000	0.145947	0.9213		NM_024906	0.112508	0.805176
NM_015292	0.0434	0.97885		NM_032217	0.007878	0.982769
NM_015416	0.186646	0.895125		NM_032313	0.022058	0.984622
NM_015633	0.008581	0.837517		NM_058172	0.102533	1
NM_015989	0.084763	1		NM_133636	0.039678	0.9886
NM_016072	0.032667	0.8981		NM_139076	0.097221	0.863231
NM_016123	0.117487	0.988143		NM_139211	0.1775	0.804828
NM_016551	0.020333	0.895		NM_144721	0.111194	0.889731
NM_017822	0.103625	0.857226		NM_145263	0.140314	0.883714
NM_018164	0.008744	0.842172		NM_152540	0.191282	0.92025
NM_018448	0.008755	0.874583		NM_152545	0.064331	0.833222
NM_018663	0.119717	1		NM_152770	0.101974	0.949375
NM_020142	0.078014	0.860361		NM_152995	0.079381	0.964286
NM_020183	0.046078	0.930484		NM_173468	0.144658	0.966429
NM_021238	0.159419	0.89335		NM_173536	0.105119	0.916625
NM_023071	0.083188	0.873727		NM_173827	0.111063	0.857415
NM_023925	0.029956	0.882769		NM_175619	0.198393	0.883732
NM_024604	0.015757	0.836625		NM_181806	0.034027	0.886865
NM_024902	0.053715	0.943783		NM_000082	0.018714	0.874385
NM_031292	0.184007	0.841222		NM_000163	0.046298	0.9028
NM_032256	0.084987	0.8055		NM_000436	0.15741	0.859115
NM_032338	0.013688	0.918882		NM_000439	0.037556	0.921313

NM_032364	0.008156	0.911133		NM_000514	0.066938	0.962774
NM_032786	0.021782	0.949087		NM_000791	0.152393	0.852462
NM_032889	0.103467	0.91716		NM_000908	0.01234	0.871311
NM_032901	0.094147	0.910533		NM_000958	0.057274	0.926231
NM_033082	0.053161	0.9428		NM_000997	0.146067	0.876723
NM_033114	0.044189	0.947067		NM_001025	0.045707	0.813173
NM_033276	0.052516	0.90769		NM_001207	0.05775	0.914053
NM_033647	0.016067	0.913043		NM_001343	0.038476	0.933345
NM_052885	0.116079	0.969864		NM_001867	0.157391	0.913364
NM_134323	0.00466	0.870182		NM_001884	0.151369	0.917857
NM_138473	0.090539	0.914457		NM_001992	0.109426	0.912875
NM_144576	0.182468	0.873		NM_002184	0.043676	0.866615
NM_144593	0.054578	0.907419		NM_002495	0.057377	0.930667
NM_152320	0.10504	0.912609		NM_002853	0.046168	0.90668
NM_152440	0.166566	0.91839		NM_003187	0.035146	0.8799
NM_153026	0.0085	0.933886		NM_003664	0.026463	0.857167
NM_153377	0.062629	0.906391		NM_003719	0.04709	0.939417
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NM_173802	0.14663	0.9465		NM_004465	0.032061	0.853065
NM_178169	0.048341	1		NM_004520	0.135278	0.878833
NM_181711	0.07323	0.898339		NM_004607	0.140526	1
NM_181847	0.061758	0.9653		NM_004932	0.185765	0.85695
NM_015070	0.089661	0.959125		NM_004934	0.156075	0.860231
NM_006370	0.188061	0.973208		NM_005711	0.04937	0.853818
NM_001176	0.12238	0.85		NM_005713	0.076229	0.909091
NM_145059	0.175763	0.89219		NM_005779	0.182225	0.876
NM_173803	0.080336	0.847368		NM_005869	0.04111	0.930125
NM_173806	0.15776	0.858857		NM_006251	0.000587	0.990476
NM_000286	0.069384	0.889455		NM_006451	0.179455	0.958789
NM_000382	0.016112	0.930542		NM_006633	0.084513	0.959029
NM_000386	0.172425	0.948692		NM_012081	0.109412	0.869375
NM_000988	0.110247	0.928938		NM_012176	0.098	0.981318
NM_001045	0.134184	0.878595		NM_013235	0.017955	0.967667
NM_001070	0.025835	0.911231		NM_013409	0.000841	0.831533
NM_001304	0.092385	0.859111		NM_014473	0.122413	0.94605
NM_001372	0.17918	0.980256		NM_014639	0.00388	0.980422
NM_001932	0.037488	0.94964		NM_014899	0.047744	0.875
NM_002230	0.140475	0.955603		NM_015084	0.137419	0.961167
NM_002795	0.000995	0.942857		NM_015342	0.015409	0.827526

NM_002809	0.040726	0.853471		NM_015360	0.011647	0.842435
NM_002878	0.194514	0.965909		NM_015577	0.028704	0.905556
NM_003010	0.079139	0.989474		NM_016218	0.004123	0.969467
NM_003079	0.02572	0.929421		NM_018046	0.045559	0.953867
NM_003110	0.065424	0.86625		NM_018268	0.054992	0.924625
NM_003204	0.055766	0.816125		NM_018356	0.036216	0.982622
NM_003559	0.185315	0.839429		NM_018695	0.005916	0.9778
NM_003876	0.074045	0.945782		NM_019072	0.006	0.912607
NM_004090	0.080792	0.86752		NM_020801	0.025866	0.9205
NM_004169	0.187321	0.871578		NM_022483	0.031324	0.934211
NM_004207	0.180306	1		NM_022913	0.006788	0.960938
NM_004217	0.161564	0.887167		NM_023039	0.030816	0.87
NM_004247	0.05772	0.900857		NM_024615	0.076856	0.997345
NM_004583	0.1604	0.864016		NM_024717	0.009706	0.916727
NM_004589	0.037792	0.81075		NM_024754	0.120074	0.917647
NM_004618	0.079222	0.937231		NM_024941	0.011495	0.987167
NM_004773	0.097299	0.83961		NM_031482	0.139576	0.8478
NM_004853	0.0036	0.954167		NM_032042	0.0848	0.952
NM_004871	0.099439	0.881778		NM_032175	0.032891	0.948778
NM_005148	0.173659	0.908111		NM_032280	0.184917	0.914068
NM_005175	0.165779	0.953		NM_032290	0.023779	0.854125
NM_005374	0.186759	0.976258		NM_032380	0.047214	0.939235
NM_005702	0.178302	0.94812		NM_130767	0.065186	0.918
NM_005854	0.119142	0.859343		NM_133433	0.000291	0.9515
NM_006041	0.03439	0.984621		NM_138453	0.009503	0.803862
NM_006042	0.148238	0.915105		NM_139168	0.031267	0.973154
NM_006546	0.029727	0.8778		NM_144722	0.094303	0.890667
NM_006804	0.115839	0.854607		NM_144725	0.048901	0.959591
NM_006807	0.072386	0.901655		NM_152295	0.074692	0.888579
NM_007026	0.008711	0.853182		NM_152403	0.097297	0.846462
NM_007144	0.001244	0.871643		NM_152405	0.108927	0.920583
NM_012138	0.027601	0.859656		NM_152623	0.037028	0.971059
NM_012393	0.001392	0.979931		NM_152756	0.00122	0.985143
NM_012448	0.08378	0.854848		NM_153013	0.18621	0.967706
NM_012481	0.137014	1		NM_153188	0.072859	0.981958
NM_013323	0.135904	0.816906		NM_153354	0.078775	0.979563
NM_013351	0.105398	0.8666		NM_153361	0.039812	0.840778
NM_013975	0.082441	0.820389		NM_153485	0.050609	0.946429
NM_014726	0.07402	0.880607		NM_153706	0.185859	0.924056
NM_014859	0.175659	0.827745		NM_173514	0.162709	0.973913

NM_014897	0.142989	0.901565		NM_173665	0.12236	0.900727
NM_015510	0.069035	0.951613		NM_173829	0.004364	0.97725
NM_016016	0.092926	0.848429		NM_175921	0.063443	0.822917
NM_016231	0	0.9332		NM_176806	0.19797	0.829176
NM_017758	0.091213	0.913043		NM_176895	0.054473	0.988457
NM_018307	0.071197	0.971444		NM_178532	0.029702	0.841917
NM_018405	0.176672	0.8412		NM_181501	0.052351	0.961125
NM_018428	0.140867	0.956522		NM_182977	0.036466	0.84375
NM_020233	0.140851	0.95		NM_025218	0.117648	0.890667
NM_020405	0.052398	0.93325		NM_000168	0.050983	0.899767
NM_020772	0.036364	0.941424		NM_000712	0.094477	0.904605
NM_020889	0.044762	0.813685		NM_002787	0.004198	0.940333
NM_021628	0.006292	0.8451		NM_002835	0.092743	1
NM_021939	0.02031	0.856433		NM_004760	0.084421	0.868333
NM_024683	0.182243	0.96332		NM_012479	0.095199	0.809457
NM_024864	0.07438	0.833939		NM_015052	0.05623	0.814897
NM_025267	0.030928	0.975529		NM_015641	0.142683	0.852952
NM_031934	0.18301	0.869102		NM_015983	0.130885	0.85228
NM_032141	0.137042	0.968667		NM_017920	0.073394	0.934532
NM_032322	0.149417	0.928607		NM_018224	0.095339	0.86087
NM_032875	0.029765	0.873		NM_024054	0.070289	0.941176
NM_033133	0.084745	0.924588		NM_024653	0.168882	0.98
NM_052857	0.034803	0.874737		NM_024963	0.11953	0.916688
NM_133439	0.083907	0.985026		NM_032014	0.141765	0.975408
NM_138355	0.140196	0.823429		NM_053043	0.115661	0.847897
NM_138463	0.011524	0.803		NM_138701	0.176534	0.907231
NM_139034	0.008599	0.923077		NM_173678	0	0.938773
NM_139280	0.121105	0.868237		NM_138462	0.173671	1
NM_144775	0.014529	0.897321		NM_000033	0.053766	1
NM_144997	0.059693	0.863		NM_000202	0.119048	0.802778
NM_145654	0.136016	1		NM_001167	0.019231	0.888933
NM_145663	0.141108	0.929306		NM_005229	0.106383	0.875
NM_145691	0.010506	0.923339		NM_013444	0.071429	1
NM_148172	0.032956	0.912986		NM_024082	0.172681	1
NM_152270	0.03294	0.919281		NM_178124	0.090852	0.868579
NM_152343	0.177046	0.881824		NM_003140	0.057951	0.80341
NM_152347	0.063795	0.890897		NM_003411	0.016023	1
NM_152464	0.001461	0.922435		NM_004681	0.03587	0.9815

Human_FM and Chimp_FM refer to the fractional methylation levels in the human and chimpanzees, respectively.

Table S5. Six Genes for which the Human Promoters Exhibit Hypermethylation Compared to the Chimpanzee Promoters

Gene	Human_FM	Chimp_FM
NM_000413	0.9023	0.1951
NM_001638	0.9813	0.0090
NM_001872	0.9259	0.0137
NM_003493	0.9848	0.1450
NM_005435	1	0.1334
NM_145064	0.8191	0.0350

Table S6. Genes Whose Promoters Are Differentially Methylated between the Human and Chimpanzee Brains Using the Second Criterion (n = 1055) Are Enriched in Similar Gene Ontology (GO) Terms as the First Set

GO Terms	Accession	p Value (FDR)
cellular process	GO:0009987	7.4e-12
protein binding	GO:0005515	1.7e-09
cellular macromolecule metabolic process	GO:0044260	2.1e-07
cellular metabolic process	GO:0044237	3.3e-07
catalytic activity	GO:0003824	1.5e-06

Table S7. Genes Whose Promoters Are Differentially Methylated between the Human and Chimpanzee Brains Using the Second Criterion (n = 1,055) Are Also Associated with Neurological Diseases, Psychological Disorders, and Cancers.

Category	Count	Fold Enrichment	Genes
cocaine abuse	3	6.2	NM_001045, NM_004898, NM_002616
attention deficit hyperactivity disorder	6	2.4	NM_000514, NM_001045, NM_002506, NM_015722, NM_002686, NM_000744
autism	9	2.3	NM_019859, NM_000807, NM_001094, NM_000561, NM_001045, NM_000267, NM_183377, NM_004898, NM_173536, NM_002616
Chemodependency	18	1.7	NM_000807, NM_019859, NM_000335, NM_005432, NM_004898, NM_000812, NM_173536, NM_002390, NM_002616, NM_001045, NM_000561, NM_006105, NM_000690, NM_005957, NM_004272, NM_000849, NM_004291, NM_000744
cancer	56	1.2	NM_002634, NM_000267, NM_000222, NM_002907, NM_000791, NM_002253, NM_002878, NM_000075, NM_172212, NM_003250, NM_005957, NM_000849, NM_033360, NM_030762, NM_004725, NM_000179, NM_007211, NM_001071, NM_005086, NM_000376, NM_000561, NM_006160, NM_001067, NM_002011, NM_016123, NM_006665, NM_005432, NM_032991, NM_015641, NM_005235, NM_018127, NM_004083, NM_012481, NM_004456, NM_004985, NM_004324,

			NM_013975, NM_002474, NM_002994, NM_000456, NM_001239, NM_002524, NM_006206, NM_006003, NM_000163, NM_004448, NM_000938, NM_030665, NM_002686, NM_022406, NM_001045, NM_004169, NM_000690, NM_006804, NM_001553, NM_016218, NM_024757
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