

Table S-1. cg13249593 is in predicted enhancer (GH17J041546) for several genes.

Gene	Description	Category	GIFtS	Relevance Score
<i>ACLY</i>	ATP Citrate Lyase	Protein Coding	50	1.07
<i>STAT5A</i>	Signal Transducer And Activator Of Transcription 5A	Protein Coding	50	1.07
<i>KRT14</i>	Keratin 14	Protein Coding	49	1.07
<i>SMARCE1</i>	SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily E, Member 1	Protein Coding	47	1.07
<i>KRT19</i>	Keratin 19	Protein Coding	46	1.07
<i>NAGLU</i>	N-Acetyl-Alpha-Glucosaminidase	Protein Coding	45	1.07
<i>KRT9</i>	Keratin 9	Protein Coding	44	1.07
<i>CAVIN1</i>	Caveolae Associated Protein 1	Protein Coding	43	1.07
<i>KRT15</i>	Keratin 15	Protein Coding	41	1.07
<i>KLHL10</i>	Kelch Like Family Member 10	Protein Coding	40	1.07
<i>LINC00974</i>	Long Intergenic Non-Protein Coding RNA 974	RNA Gene	16	1.07
<i>ENSG00000267758</i>	Novel Transcript	RNA Gene	9	1.07
<i>HSALNG0116441</i>		RNA Gene	5	1.07
<i>piR-48749-021</i>		RNA Gene	4	1.07
<i>LOC116276463</i>	CRISPRi-Validated Cis-Regulatory Element Chr17.2497	Biological Region	2	0.93

Abbreviations: GIFtS, GeneCards Inferred Functionality Scores.

Table data from <https://www.genecards.org/Search/Keyword?queryString=GH17J041546>

Table S-2. TCA cell-specific DMRs.

Region chr:bp	Model	Cell type	No. CpG	Δ Meth.	p	GREAT annotation ^a	Illumina annotation		CpG Island
						Gene (Dist. to TSS)	Gene	Feature	
1:161008461_161008826	R0-NR0	CD8T	8	hyper	9.5e-18		TSTD1	TS200	Island
12:9217389_9_217907	R0-NR0	Bcell	10	hyper	5.8e-15		LOC144571	TS200	Island
1:202310823_202311278	R1-NR1	Neu	7	hyper	3.1e-14		UBE2T	TS200	Island
17:6899084_6_899577	R1-NR1	Mono	11	hyper	2.0e-13	ALOX12 (-53)	ALOX12	TS200	Island
13:36871753_36872346	R1-R0	NK	9	hypo	8.6e-13		C13orf38	TS200	Island
1:161008461_161008826	R0-NR0	CD4T	8	hypo	1.8e-12		TSTD1	TS200	Island
17:6899084_6_899577	R1-NR1	NK	11	hypo	4.9e-12	ALOX12 (-53)	ALOX12	TS200	Island
10:77542301_77542585	R0-NR0	CD4T	9	hyper	1.5e-11		C10orf11	TS200	OpenSea
6:32063725_3_2064258	R1-NR1	NK	16	hypo	5.9e-11	TNXB (-50087)	TNXB	Body	Island
6:31148331_3_1148748	R0-NR0	CD8T	15	hyper	1.2e-10				Island
13:111267666_111268031	R1-NR1	Bcell	10	hypo	1.1e-10		CARKD	TS200	Island
6:30881463_3_0881920	R0-NR0	NK	22	hypo	2.0e-10		VARS2	TS200	Island
8:22132664_2_2133004	R0-NR0	CD8T	9	hypo	2.0e-10		PIWIL2	TS200	Island
12:9217509_9_217907	R0-NR0	CD8T	9	hypo	9.9e-10		LOC144571	TS200	Island
19:55549589_55549842	R1-NR1	Mono	7	hypo	9.8e-10		GP6	TS200	OpenSea
6:30419490_3_0419576	R0-NR0	CD4T	5	hypo	4.0e-10				Island
16:1030387_1_030619	R0-NR0	CD4T	7	hyper	4.5e-09	SOX8 (-1305)	SOX8	TSS1500	Island
10:42862875_42863444	R1-NR1	NK	5	hypo	1.4e-08		LOC441666	Body	Island
2:21266726_2_1266995	R0-NR0	NK	6	hypo	7.5e-09	APOB (+84)	APOB	TS200	Island
2:43903581_4_3903842	R1-NR1	Bcell	3	hyper	1.7e-08		PLEKHH2;L OC728819	TS200	OpenSea
6:1604012_16_04212	NR1-NR0	Mono	5	hypo	1.3e-08				N_Shore
12:52473421_52473731	R1-NR1	Bcell	4	hyper	2.3e-08				Island
2:109746690_109746754	R1-R0	Neu	4	hyper	5.6e-09		LOC100287 216;SH3RF3	TS200	Island

Region chr:bp	Model	Cell type	No. CpG	Δ Meth.	GREAT annotation ^a		Illumina annotation		
					<i>p</i>	Gene (Dist. to TSS)	Gene	Feature	CpG Island
19:54106592_54106876	NR1-NR0	Mono	3	hypo	2.5e-08		LOC284379	TS200	OpenSea
13:23309929_23310464	R1-NR1	Bcell	5	hyper	5.2e-08				OpenSea
16:54210495_54210550	R0-NR0	NK	2	hypo	6.5e-09				OpenSea
6:30419490_30419576	R0-NR0	Bcell	5	hyper	2.2e-08				Island
17:41438329_41438402	R0-NR0	CD8T	3	hyper	2.1e-08				Island
10:8096632_8096818	R1-NR1	Bcell	5	hypo	3.3e-07		FLJ45983	TS200	Island
11:117069848_117070046	R1-NR1	NK	4	hypo	5.5e-07		TAGLN	TS200	OpenSea
6:32847761_32847845	R0-NR0	NK	6	hypo	4.7e-06		PPP1R2P1	Body	Island
22:31318239_31318373	R1-NR1	Bcell	3	hypo	2.8e-05		C22orf27	TS200	Island
3:159557778_159557797	R1-NR1	NK	2	hypo	3.7e-05	SCHIP1 (+138)	SCHIP1	Body	OpenSea
2:113993051_113993142	R1-NR1	Bcell	2	hyper	5.2e-04		PAX8; LOC440839; LOC654433	Body;Body; Body;Body; Body;Body; TSS1500	N_Shore
6:31939279_31939322	NR1-NR0	Mono	3	hypo	3.6e-04		STK19;DOM 3Z	TSS1500;TS S1500;Body; Body	N_Shore
4:103940922_103940950	R0-NR0	Bcell	2	hypo	2.8e-04		NHEDC1;NH EDC1	TS200	Island
6:32121112_32121204	R1-NR1	Neu	5	hypo	4.6e-03		PPT2;PRRT 1	TS200	N_Shore
11:86383235_86383241	R1-NR1	Bcell	2	hypo	5.1e-03		ME3	TS200	Island
20:3052114_3052151	R1-R0	NK	2	hypo	4.2e-03	OXT (-133)	OXT	TS200	Island

Abbreviations: bp, base pair; chr; chromosome; CI, Confidence Interval; FDR, false discovery rate; GREAT, Genomic Regions Enrichment of Annotations Tool; Hyper, Hypermethylation; Hypo, Hypomethylation; NR, treatment non-responder; R, treatment responder; T₀, baseline visit.

^a Distance from CpG to transcription start site of nearest upstream and downstream gene from rGREAT.

Table S-3. Results from analyses among self-report white participants for *limma* DMP results with $p < 1 \times 10^{-6}$.

CpG	Model ^b	Primary Analyses		Within self-report white participants only	
		% Δ Beta	<i>p</i>	% Δ Beta	<i>p</i>
cg06336912	T ₁ : R-NR	-5.86	6.5e-6	-6.49	6.2E-06
cg15936718	T ₁ : R-NR	-3.49	8.9e-6	-3.72	2.8E-05
cg16868591	(R ₁ -R ₀)-(NR ₁ -NR ₀)	-3.39	3.0e-6	-3.24	2.5E-05
cg19506849	R ₁ -R ₀	2.64	9.4e-6	2.63	1.4E-06
cg18224793	NR ₁ -NR ₀	2.34	4.7e-6	2.34	2.6E-06

Abbreviations: bp, base pair; chr; chromosome; CI, Confidence Interval; FDR, false discovery rate; GREAT, Genomic Regions Enrichment of Annotations Tool; NR, treatment non-responder; R, treatment responder; T₀, baseline visit.

^a Distance from CpG to transcription start site of nearest upstream and downstream gene from rGREAT.

Table S-4. Results from analyses among self-report white participants for *TCA* DMP analyses.

CpG	Model	Analysis	Cell type	Δ Meth.	Joint model	Marginal conditional model p-value
cg13249593	T ₀ : R-NR	Primary	CD4T	0.226	<i>p</i> : 2.4E-8	4.6E-6
			CD8T	-0.310	<i>p</i> _{FDR} : 9.5E-3	1.8E-5
			NK	-0.489		2.3E-6
		Within self-report white participants	CD4T	0.217	<i>p</i> : 4.8E-7	3.8E-5
			CD8T	-0.315	<i>p</i> _{FDR} : 0.957	5.0E-5
			NK	-0.501		2.6E-5

Abbreviations: FDR, false discovery rate; GREAT, Genomic Regions Enrichment of Annotations Tool; NR, treatment non-responder; R, treatment responder; T₀, baseline visit.

^a Distance from CpG to transcription start site of nearest upstream and downstream gene from rGREAT.

^b Model comparing difference in DNA methylation baseline before MTX treatment between those were identified as treatment responders compared to non-responders.

^c Joint model from tensor composition analysis tests for evidence of differential methylation within any cell-type at each CpG.

Table S-5. Meta analysis results for *limma* DMP results with $p < 1 \times 10^{-6}$.

CpG	Model ^b	Primary Analyses		Meta-analyses ^a		
		% Δ Beta	<i>p</i>	% Δ Beta	<i>p</i>	<i>p_Q</i> ^b
cg06336912	T ₁ : R-NR	-5.86	6.5e-6	-5.00	2.0E-08	0.84
cg15936718	T ₁ : R-NR	-3.49	8.9e-6	-5.58	7.4E-04	0.84
cg16868591	(R ₁ -R ₀)- (NR ₁ -NR ₀)	-3.39	3.0e-6	-4.36	1.5E-05	0.71
cg19506849	R ₁ -R ₀	2.64	9.4e-6	2.38	9.5E-04	0.94
cg18224793	NR ₁ -NR ₀	2.34	4.7e-6	1.95	2.7E-03	0.70

Abbreviations: bp, base pair; chr; chromosome; CI, Confidence Interval; FDR, false discovery rate; GREAT, Genomic Regions Enrichment of Annotations Tool; NR, treatment non-responder; R, treatment responder; T₀, baseline visit.

^a Inverse variance-meta analysis with random effect, calculated using Meta R package.

^b P-value for Cochran's Q heterogeneity test. *I*² estimated to be 0 for all CpGs in this table.