

Supplementary table 1. Group Characteristics.

	Discovery	Replication 1	Replication 2
Sex			
Female (N)	466	202	337
Male (N)	141	77	0
M:F ratio	0.30	0.38	0
Group			
MS Case (N)	208	140	235
Non-MS Control (N)	402	139	102
Case:Control ratio	0.52	1.01	2.30
Age			
Mean (\pm SD)	38.8 (\pm 9.4)	41.2 (\pm 11.2)	51.8 (\pm 11.0)
Smoker Status (cases only)			
Ever (N)	131	71	N/A
Never (N)	75	69	N/A
No data	2	0	N/A

Supplementary Table 2: The 13 DMPs at the HLA-DRB locus in all three groups. All DMPs with $\Delta\beta > 2\%$ and genome-wide significant in the discovery group as well as $FDR \leq 0.05$ and $\Delta\beta > 2\%$ in both validation cohorts. $\Delta\beta$ = delta beta

CpG	Chr	Position	Gene	Feature	Discovery Cohort $\Delta\beta$	Discovery Cohort p-value	Validation Cohort 1 $\Delta\beta$	Validation Cohort 1 p-value	Validation Cohort 2 $\Delta\beta$	Validation Cohort 2 p-value
cg01341801	6	32489203	HLA-DRB5	Body	0.192	3.43E-11	0.212	6.51E-07	0.276	1.94E-05
cg25140213	6	32522683	HLA-DRB6	Body	0.187	3.14E-10	0.189	1.63E-06	0.238	4.55E-05
cg17369694	6	32485396	HLA-DRB5	3'UTR	0.155	2.65E-11	0.174	1.90E-06	0.217	1.46E-04
cg09139047	6	32552042	HLA-DRB1	Body	-0.135	1.36E-08	-0.162	2.70E-06	-0.175	2.70E-03
cg14645244	6	32552205	HLA-DRB1	Body	-0.122	7.18E-10	-0.131	6.30E-07	-0.128	2.46E-04
cg10632894	6	32552453	HLA-DRB1	Body	-0.12	6.55E-08	-0.127	2.01E-06	-0.207	5.35E-05
cg08845336	6	32551891	HLA-DRB1	Body	-0.119	4.01E-09	-0.14	2.16E-06	-0.137	4.94E-05
cg10104420	6	32526414	HLA-DRB6	Body	-0.107	1.96E-09	-0.135	5.60E-07	-0.071	3.11E-02
cg19575208	6	32551888	HLA-DRB1	Body	-0.105	3.55E-09	-0.121	3.26E-06	-0.128	9.10E-05
cg17416722	6	32554385	HLA-DRB1	Body	0.096	4.67E-11	0.105	1.88E-06	0.14	2.72E-04
cg00440797	6	32493873	HLA-DRB5	Body	0.079	5.40E-10	0.07	5.95E-05	0.124	1.24E-04
cg00579921	6	32489991	HLA-DRB5	Body	0.064	7.06E-08	0.051	6.31E-04	0.101	6.14E-03
cg26036029	6	32552443	HLA-DRB1	Body	-0.061	4.72E-08	-0.042	5.30E-05	-0.076	8.69E-05
cg22930808	3	12228188	PARP9	5'UTR	-0.043	6.66E-08	-0.079	8.45E-08	-0.088	5.90E-04
cg01028142	2	7004578	CMPK2	Body	-0.036	6.28E-12	-0.039	4.77E-06	-0.062	1.57E-05
cg01533966	1	90363165	LRR8D	5'UTR	0.03	1.41E-12	0.019	3.94E-02	0.03	2.47E-02

cg01311537	10	50386709	TMEM273	Body	-0.021	4.98E-08	-0.017	7.78E-03	-0.035	4.08E-03
cg10778971	14	94577101	IFI27	5'UTR	-0.02	4.43E-12	-0.014	1.15E-03	-0.014	9.12E-03

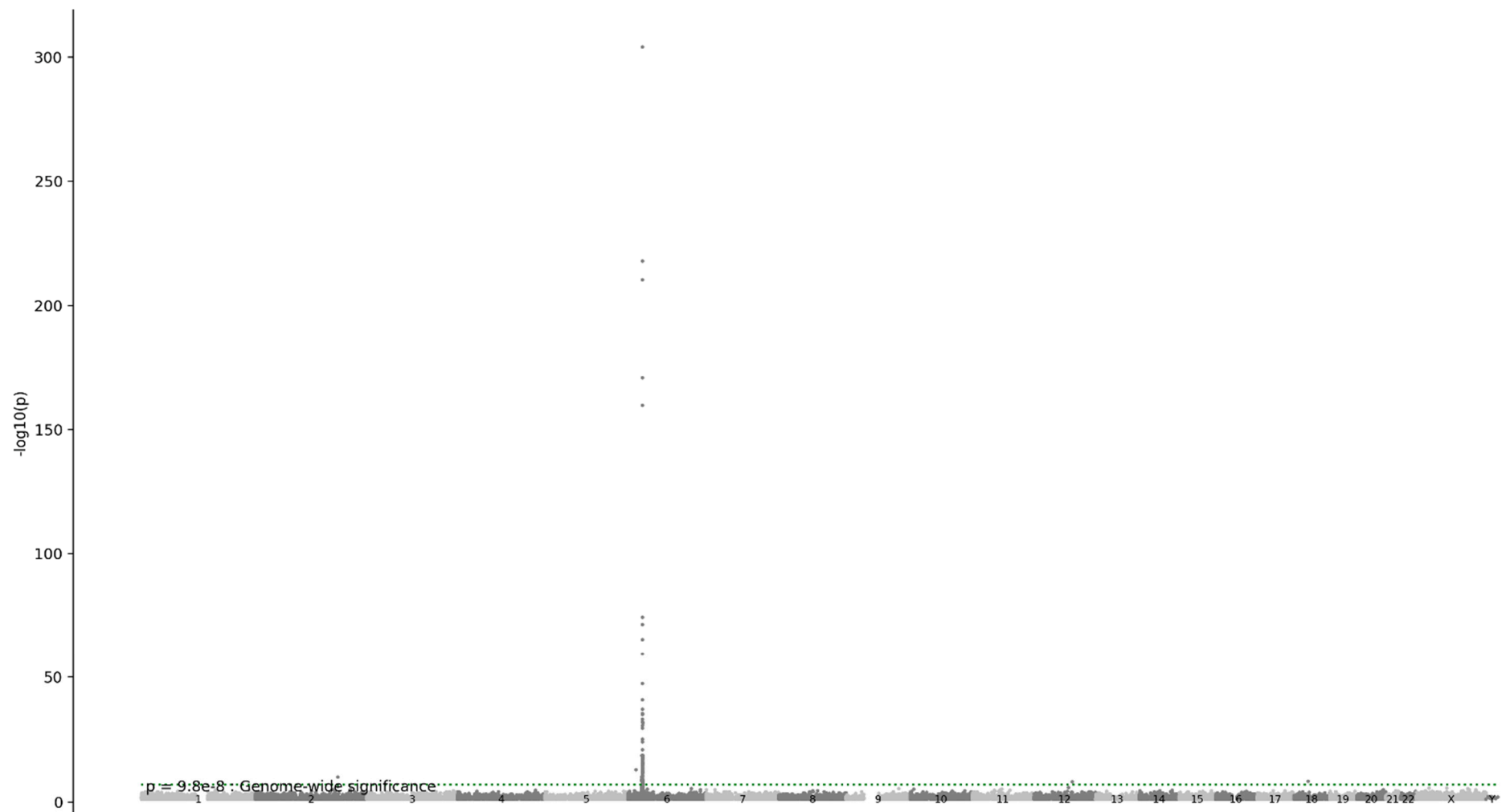
Supplementary Table 3 – IFN-related DMPs in Ausimmune before and after removal of IFN treated samples

CpG	Chromosome	Position	Gene	Only Untreated $\Delta\beta$	Only Untreated p- value	All Samples $\Delta\beta$	All Samples p-value
cg01028142	2	7004578	<i>CMPK2</i>	-0.02	3.50E-07	-0.036	6.28E-12
cg01533966	1	90363165	<i>LRRC8D</i>	0.03	2.21E-11	0.03	1.41E-12
cg10778971	14	94577101	<i>IFI27</i>	-0.01	2.06E-08	-0.02	4.43E-12
cg22930808	3	122281881	<i>PARP9</i>	-0.03	3.26E-04	-0.043	6.66E-08

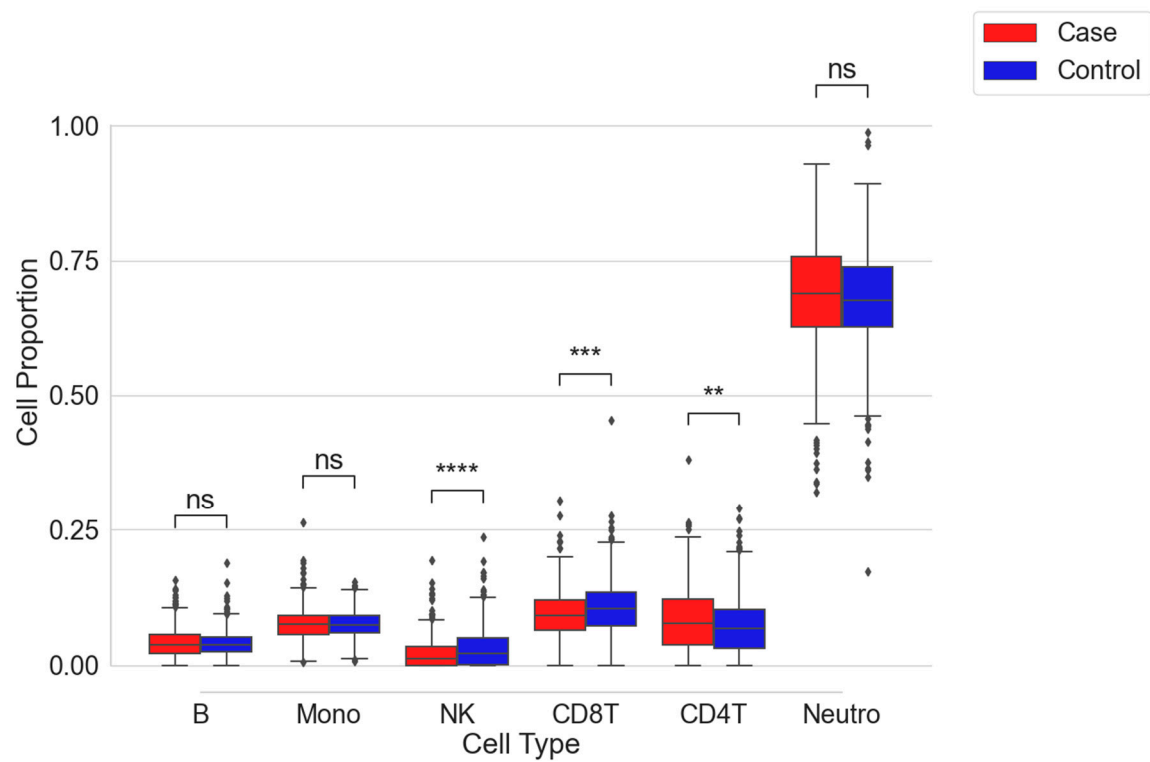
Supplementary Table 4: DMRs in the combined cohort.

Chromosome	Start	End	Width	Number of CpGs	Min Smoothed FDR	Maximum Difference	Mean Difference	Overlapping Genes	DMR Index
chr6	32548321	32550067	1747	10		0.161	0.051	HLA-DRB1	1
chr6	32551749	32552670	922	19		-0.167	-0.077	HLA-DRB1	2
chr6	32553920	32556093	2174	5		0.109	0.059	HLA-DRB1	3

chr6	32557422	32558459	1038	5	0.126	0.029	HLA-DRB1	4
chr6	32489203	32490444	1242	12	0.182	0.056	HLA-DRB5	5
chr6	32520615	32523136	2522	11	0.152	0.064	HLA-DRB6	6
chr6	32525805	32526702	898	12	0.117	0.034	HLA-DRB6	7
chr6	32604564	32610971	6408	24	0.113	0.043	HLA-DQA1	8
chr6	32632000	32636189	4190	40	-0.111	-0.012	HLA-DQB1	9

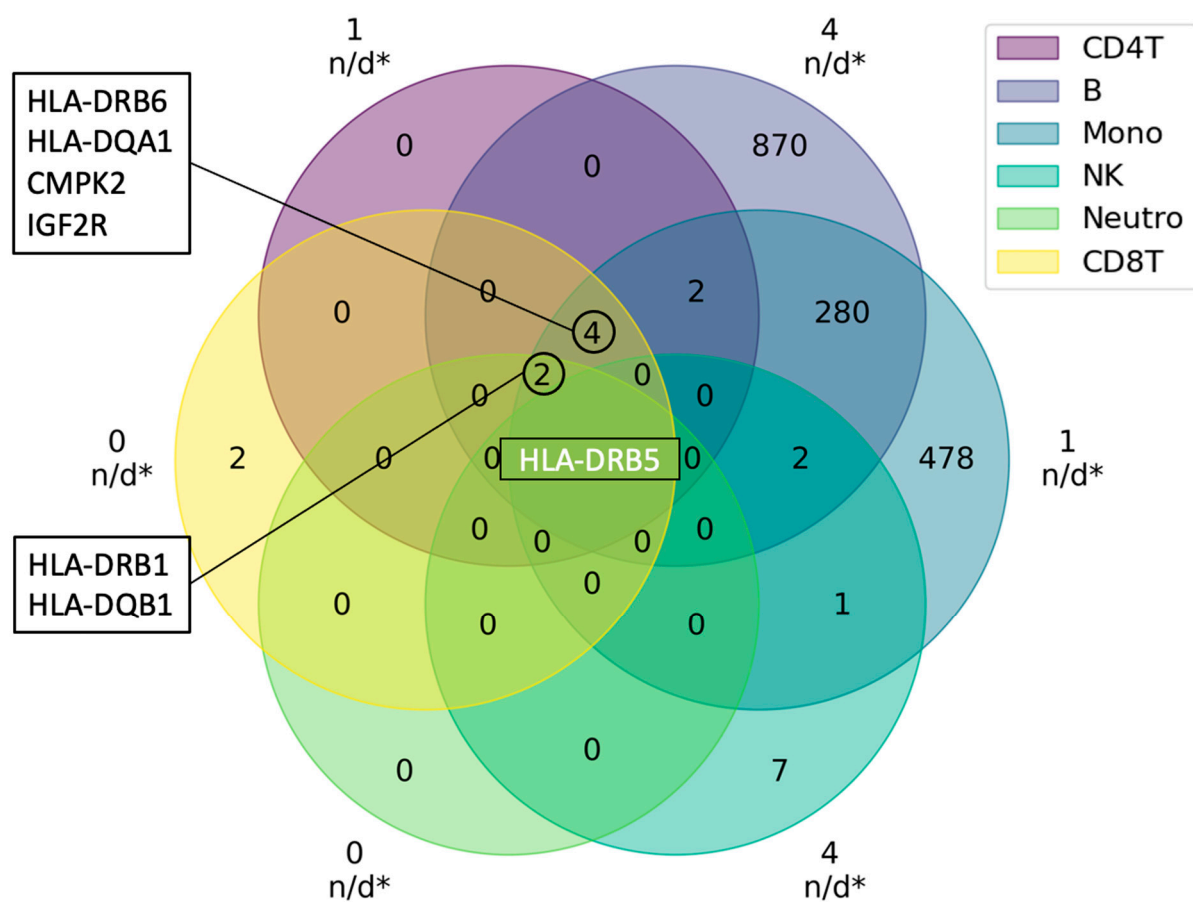


Supplementary figure 1: Manhattan plot showing the magnitude of the *HLA-DRB1 15:01* Haplotype on methylation. Each dot represents the $-\log_{10}(p\text{-value})$ of the ANOVA test between Risk Haplotype *HLA-DRB1 15:01* (Presence/Absence) and CpG. Chromosomes are shown with alternating shades of grey)



Supplemental Figure 2: Cell proportion differences between cases and controls using the combined cohort

Tukey Box Plot showing mean and interquartile range of cases (blue) and controls (orange) in all datasets. Black diamonds indicate outliers. ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, ns = not significant.



Supplementary Figure 3. Overlap of DMPs among cell subtypes. Venn diagram showing overlap of csDMPs in the combined cohort, between all the cell types. *denotes elements of set intersections that are not displayed. For example, only shared between CD4⁺T cells and NK cells.

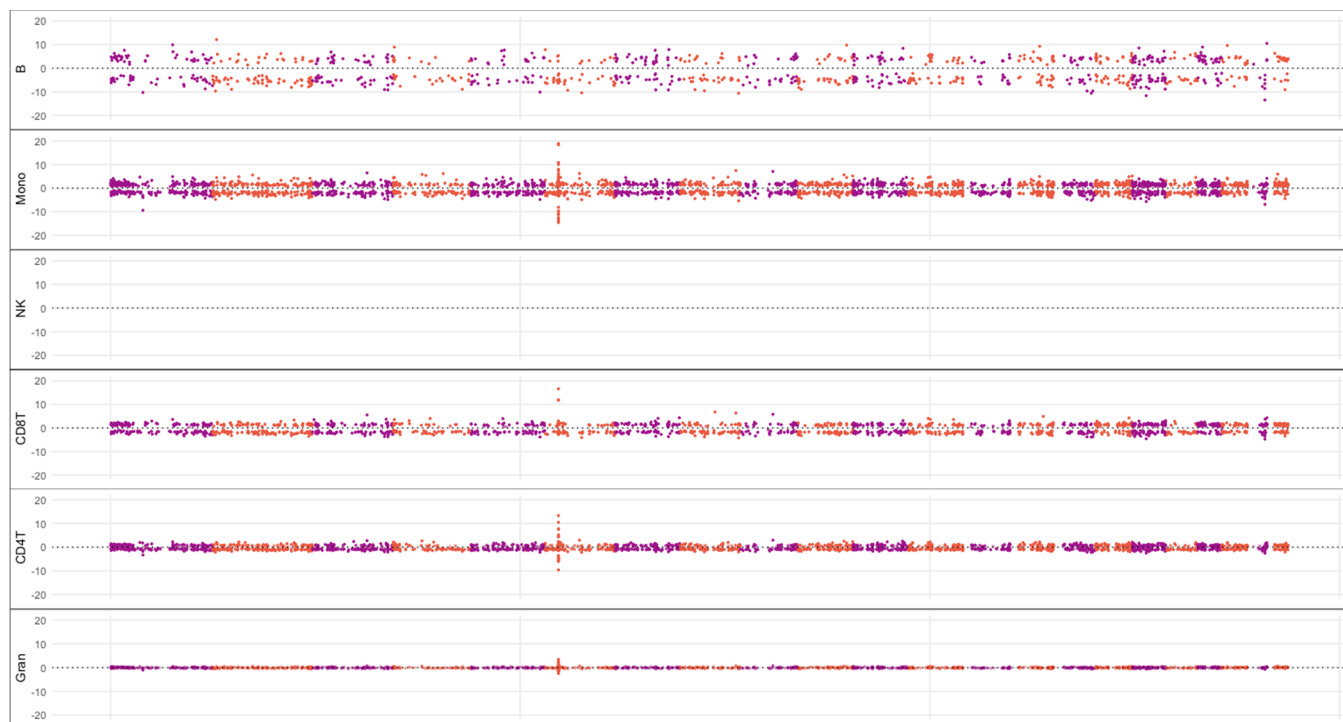
Supplementary Table 5: Overlapping csDMP effect size. Effect size, chromosome location (CHR) and gene name for the 28 csDMPs which overlap between all 4 major cell types. Red = hypomethylated blue = hypermethylated. Darker shade indicates larger effect size.

csDMP	B Cell	Mono	CD8 ⁺ T Cells	CD4 ⁺ T Cells	CHR	Position	gene
cg01028142	-4.70	-3.61	-2.06	-2.65	2	7004578	CMPK2
cg10187879	4.61	2.57	2.14	2.20	6	32223208	
cg17369694	23.92	18.85	11.44	12.80	6	32485396	HLA-DRB5
cg01341801	26.79	21.29	12.76	14.76	6	32489203	HLA-DRB5
cg26981746	12.24	9.82	5.46	6.64	6	32490012	HLA-DRB5
cg27362989	16.56	12.99	7.63	9.32	6	32492198	HLA-DRB5
cg19516921	8.63	6.97	3.90	5.11	6	32493994	HLA-DRB5
cg19774683	18.72	14.64	8.71	10.18	6	32522400	HLA-DRB6
cg25140213	16.27	12.93	7.61	8.88	6	32522683	HLA-DRB6
cg06559318	17.40	12.78	7.29	9.57	6	32526260	HLA-DRB6
cg10104420	-11.81	-8.97	-5.31	-5.91	6	32526414	HLA-DRB6
cg04422742	20.09	14.78	8.70	10.26	6	32527793	HLA-DRB6
cg26590106	16.53	12.43	7.58	9.28	6	32548321	HLA-DRB1
cg12867728	4.89	2.69	2.30	2.62	6	32549283	HLA-DRB1
cg20022036	-8.67	-5.39	-3.94	-4.52	6	32549496	HLA-DRB1
cg13910785	20.98	16.20	10.21	10.69	6	32549849	HLA-DRB1
cg11404906	-19.94	-14.89	-9.26	-10.79	6	32551749	HLA-DRB1
cg19575208	-10.61	-8.05	-4.95	-5.70	6	32551888	HLA-DRB1
cg08845336	-12.48	-9.78	-5.94	-6.93	6	32551891	HLA-DRB1
cg15568074	-22.68	-16.42	-9.60	-11.01	6	32551949	HLA-DRB1
cg16514085	-22.42	-17.84	-10.42	-11.51	6	32552152	HLA-DRB1
cg14645244	-15.93	-13.15	-7.17	-8.67	6	32552205	HLA-DRB1
cg10632894	-16.62	-13.47	-7.92	-9.55	6	32552453	HLA-DRB1
cg05383619	11.50	9.67	5.23	6.40	6	32553920	HLA-DRB1
cg17416722	16.44	13.60	7.80	9.03	6	32554385	HLA-DRB1
cg02919082	8.48	6.21	3.87	4.22	6	32605694	HLA-DQA1
cg05341252	-24.25	-17.33	-10.70	-11.03	6	32632715	HLA-DQB1
cg04733681	4.81	3.41	2.21	2.53	6	160423822	IGF2R

a)

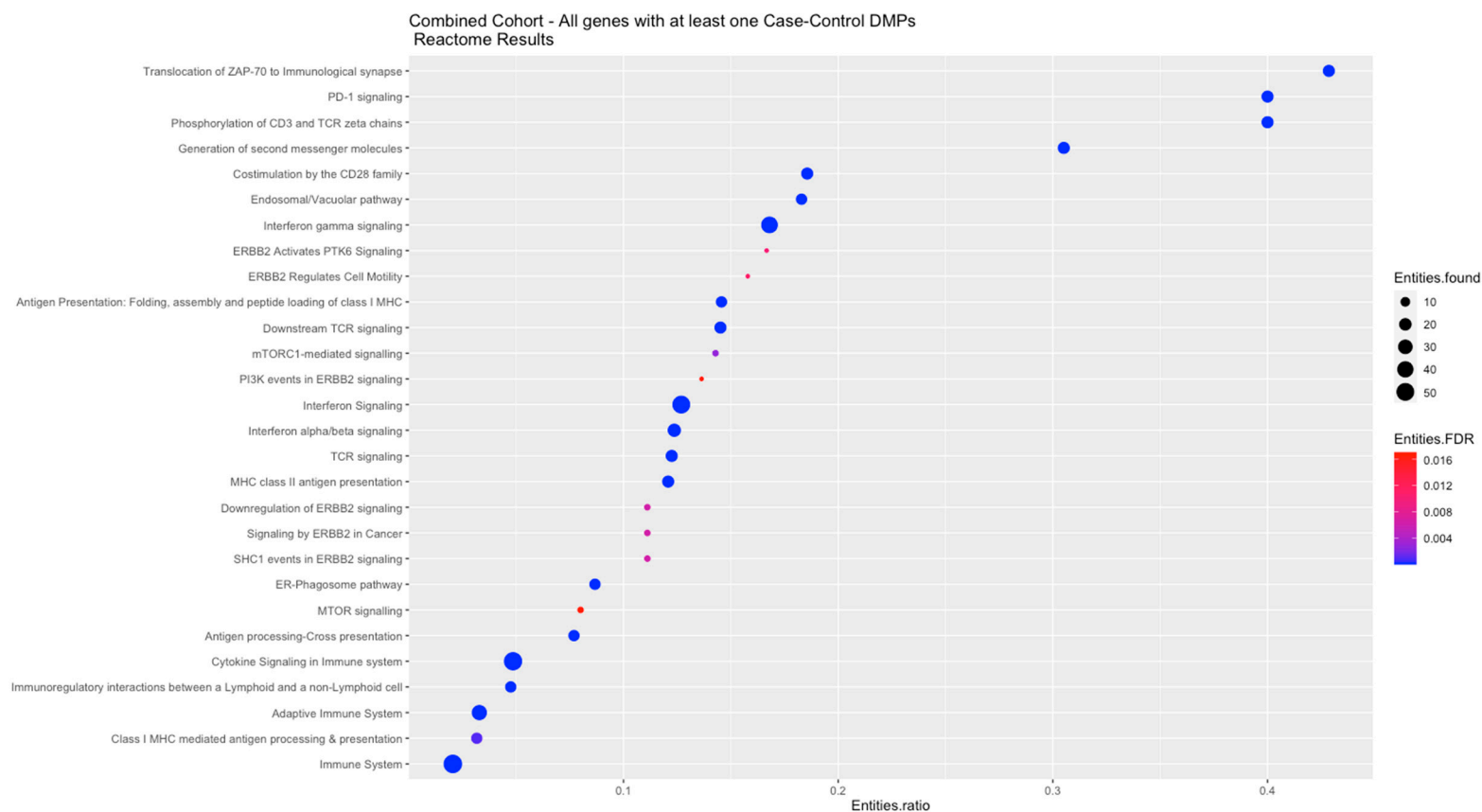
	NK	B cell	Monocytes	Neutrophils	CD8T	CD4T
Total	0	924	1327	4	475	48
Hypo	0	517	816	1	361	23
Hyper	0	407	511	3	114	25

b)



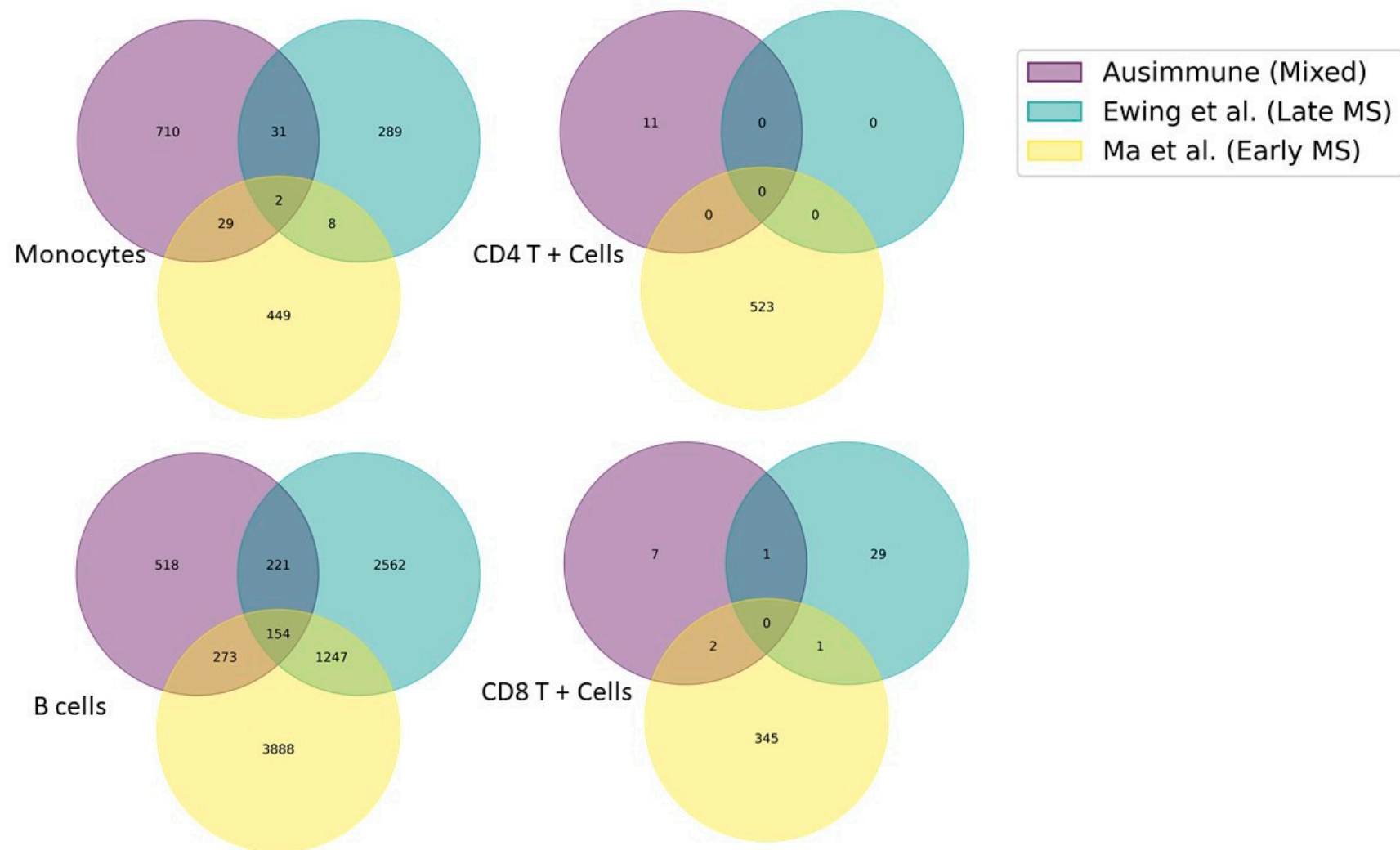
Supplementary Figure 4: Genome-wide cell-specific DNA methylation profile in discovery group only.

a) Total number of csDMPs by cell type and breakdown by hyper and hypomethylated. b) Manhattan plot representing genome-wide effect size for all csDMPs, by cell type. The Y axis represents the model estimate for effect size and X axis represents genome-coordinates, chromosomes are in chronological order and represented by alternating colors.



Supplementary Figure 5: Whole-Blood over-representation analysis

Using a ranked gene-list with 92 genes containing at least one DMP mapped to a gene with absolute $\Delta\beta$ above 2%. Y axis represents all pathways identified. X axis represents the gene ratio (number of entities in gene list vs number of entities in the pathway) for a specific pathway. Marker size represents the number of Entities. Colour represents significance.



Supplementary Figure 6: Overlap of Genes containing at least one csDMP identified in this study, Ewing et al. [47] and Ma et al. [33] Study.