DNA methylation profiles in peripheral blood CD4$^+$ lymphocytes versus brain

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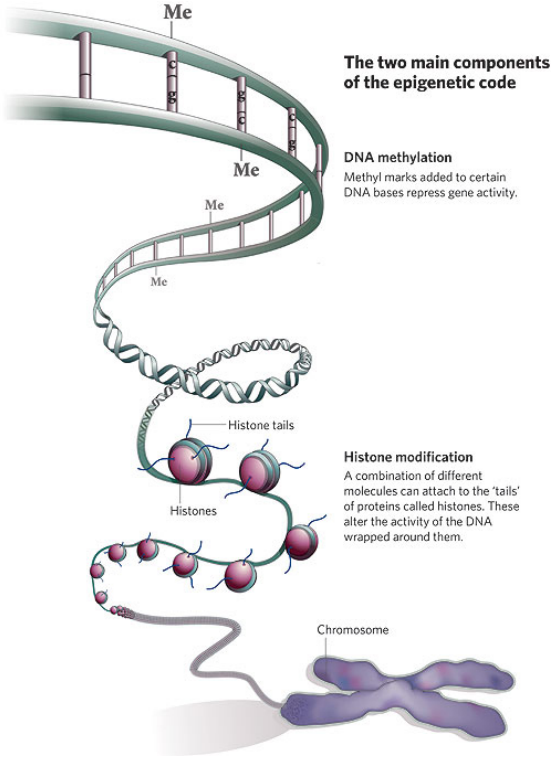
Disclosures

- I have no disclosure.

DNA methylation

- DNA methylation is a most common epigenetic marker;
- Addition of a methyl (CH3) group to DNA nucleotides.



(Qiu. 2006 *Nature*)

DNA methylation

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- Typically it acts to suppress gene transcription

DNA methylation

- DNA methylation is essential in regulating gene expression, cell differentiation and development;
- Typically it acts to silence/suppress gene transcription

Agouti (*ASPI*) mice (Waterland and Jirtle. 2003 *Mol Cell Biol*)

DNA methylation and AD

- Aberrant methylation alterations are a/w AD.
  - Neuronal immunoreactivity for DNA methylation markers are reduced in AD (Mastroeni et al. 2010 *Neurobiol Aging*).
  - Early alterations in DNA methylation in 11 loci are associated with AD pathology (De Jager et al. 2014 *Nat Neurosci*).
  - DNA methylation in AD loci are implicated in pathologic AD diagnosis (Yu et al. 2015 *JAMA Neurol*).

Complexity of interrogating DNA methylation

Tissue/Cell type specificity

- The utility of interrogating peripheral tissue for a role of DNA methylation in neurodegeneration is unclear;

DNA methylation pattern change over time

- Global methylation decreases with age (Heyn et al. 2012 *Proc Natl Acad Sci U S A*);
- Fastest changes occur during the prenatal period, slow down markedly after birth and slow further with aging (Numata et al. 2012 *Am J Hum Genet*);
- Global methylation changes over time, but some increase and some decrease (Bjornsson et al. 2008 *JAMA*).

Objectives

- Compare global features of DNA methylation;
- Examine correlations and paired difference at individual CpG sites;
- Test associations of brain methylation with AD pathology using blood data.

Methods

Subject characteristics (N=41)

- ROS & MAP subjects with methylation measured three times (T1, T2, and death);
- Age at death: 89.6 years (SD=4.9);
- 27 (65.9%) were females;
- Education: 15.2 years (SD=3.5);
- Years between T1 and T2 (Mean=7.5, SD=4.1);
- Years between T2 and death (Mean=0.9, SD=0.7);
- 25 w/dementia at death;
- 30 w/ pathologic AD diagnosis.

Methods

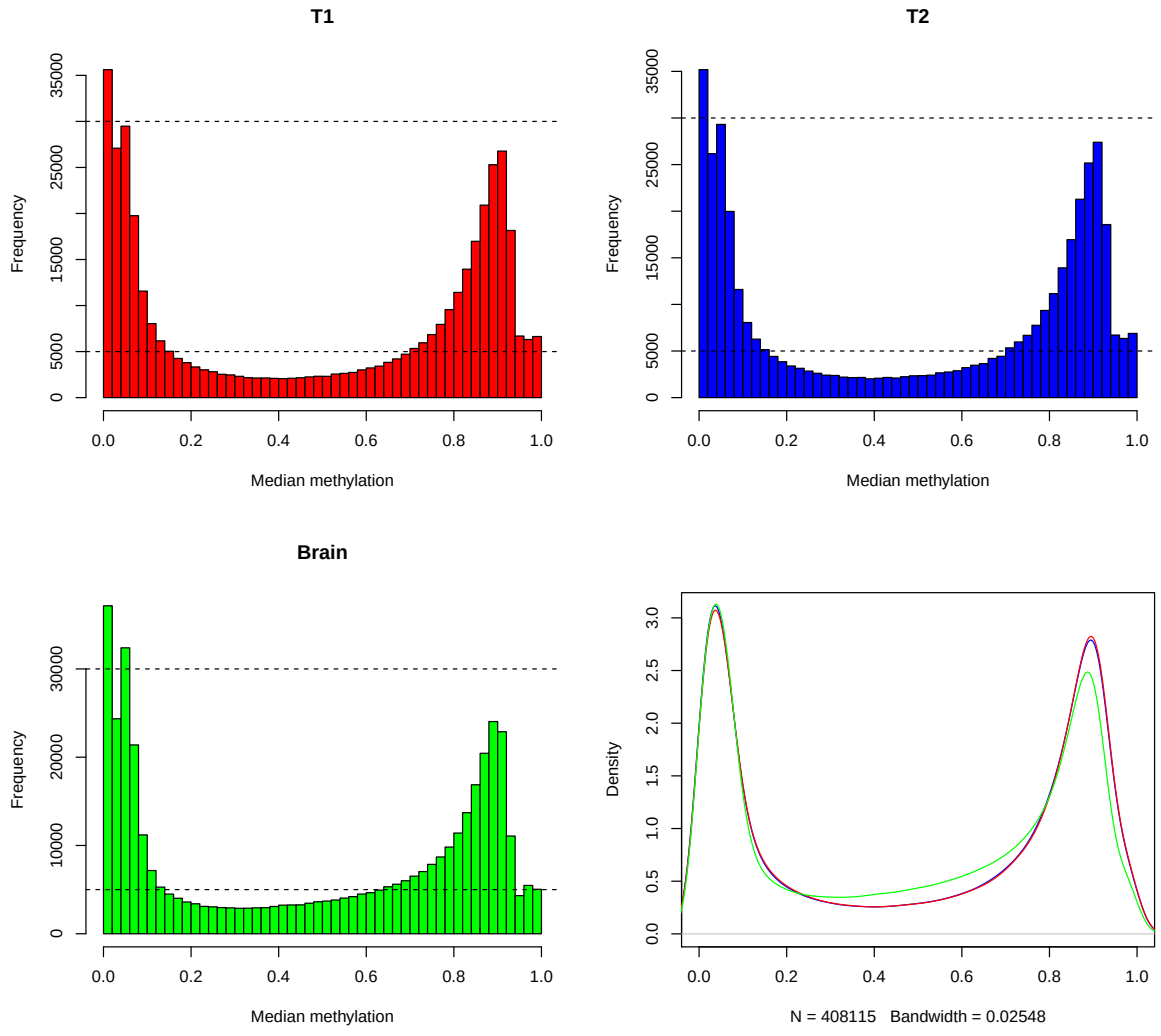
DNA methylation measures

- Blood data are from $CD4^+$ lymphocytes; brain data from DLPFC;
- Infinium HumanMethylation450 BeadChip;
- 420,132 CpG sites in autosomes;
- Methylation level as beta value (Yang et al 2015, *Int. J. Biochem. Cell Biol.*).

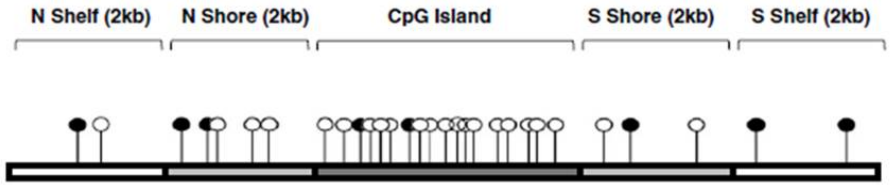
Statistical analyses

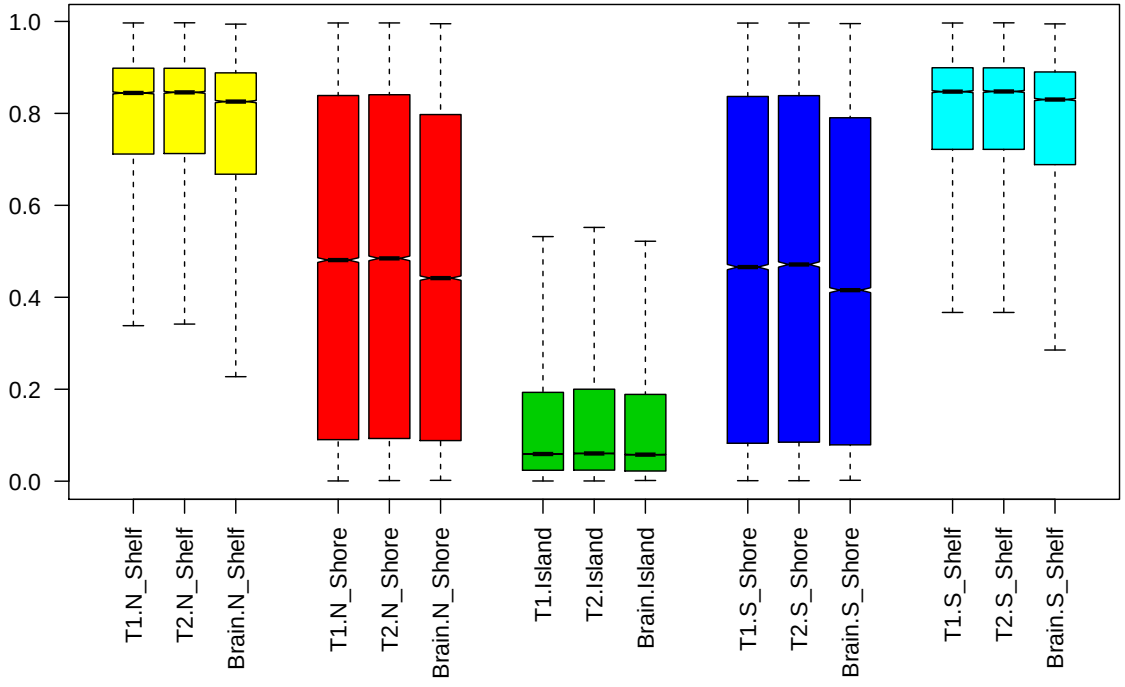
- Global features are captured by average methylation level;
- Pearson correlations and paired *t*-tests;
- Linear regression test the association with AD pathology (neuritic plaque).

Bimodal distribution of average DNA methylation across genome

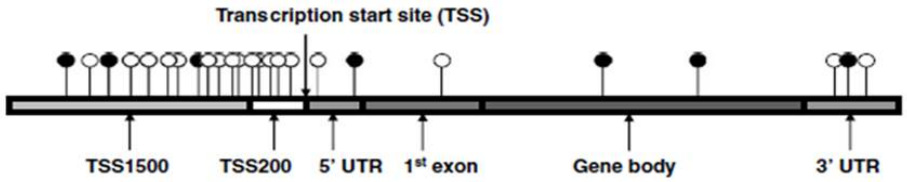


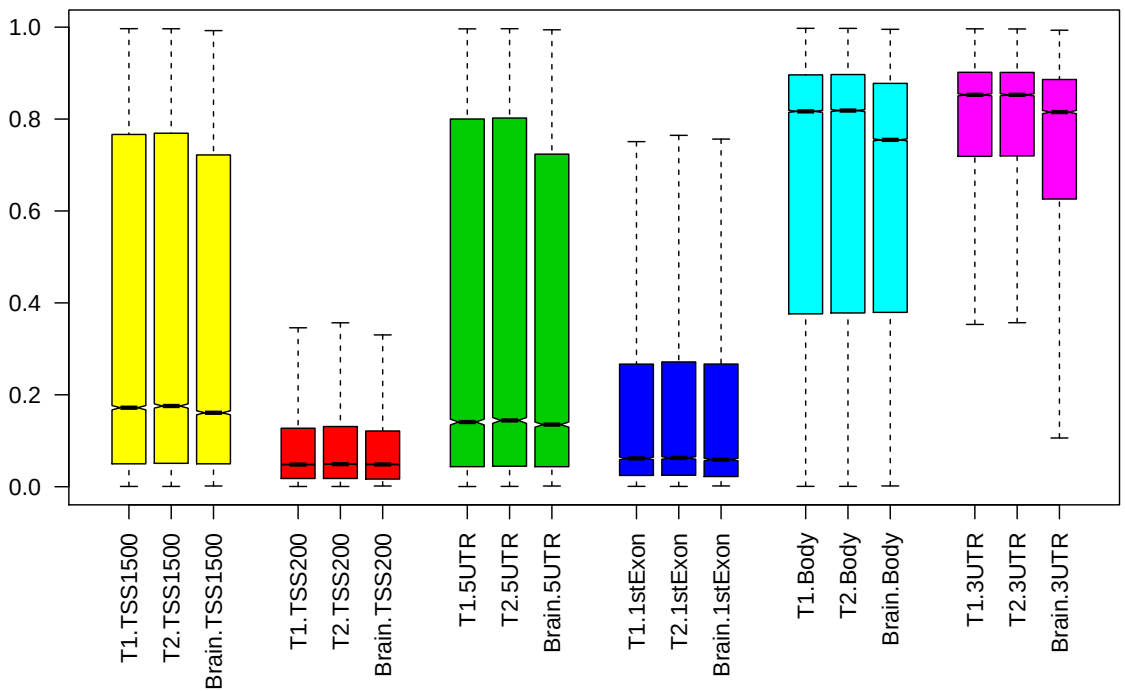
Distribution by island features



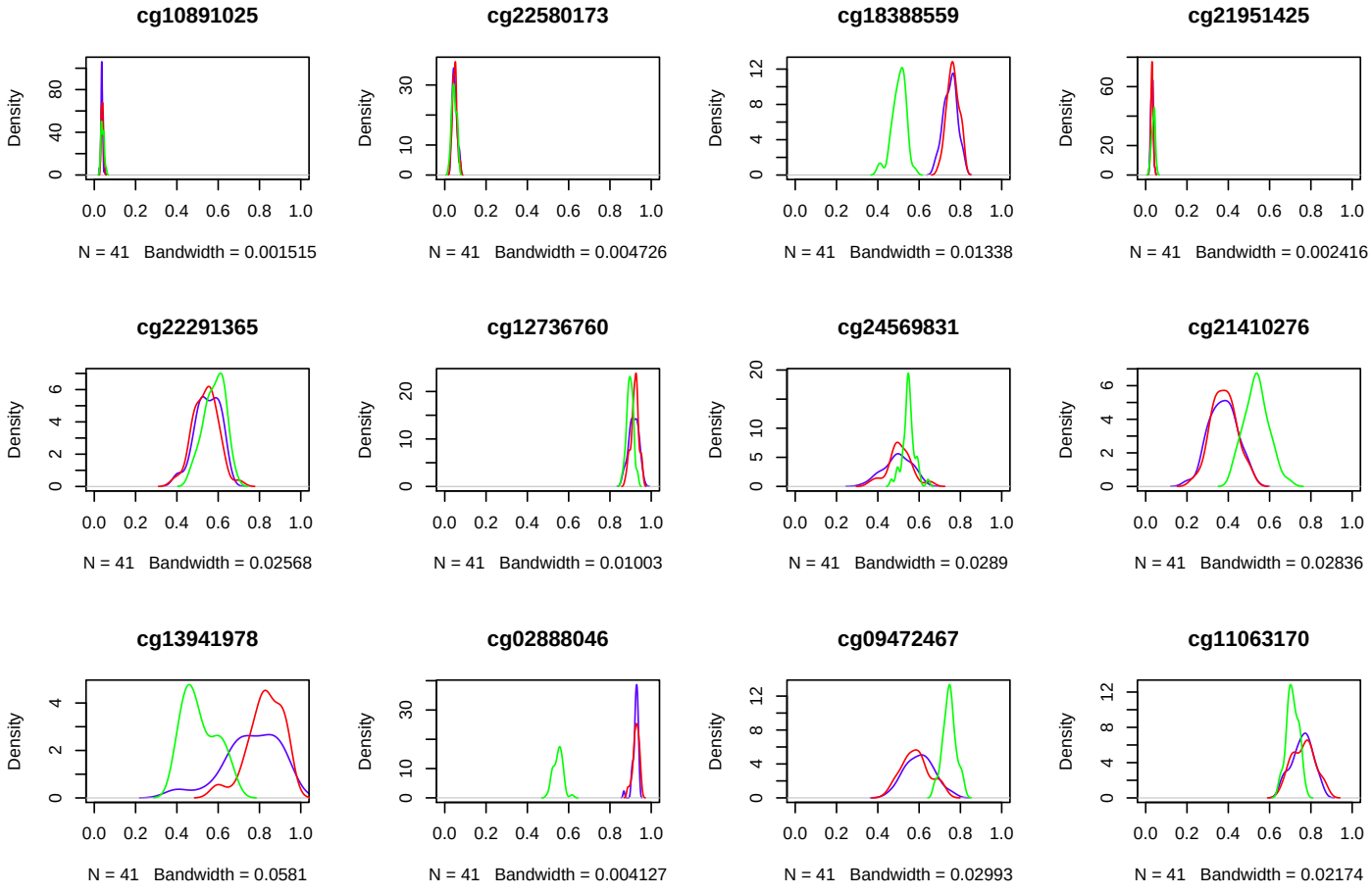


Distribution by gene features

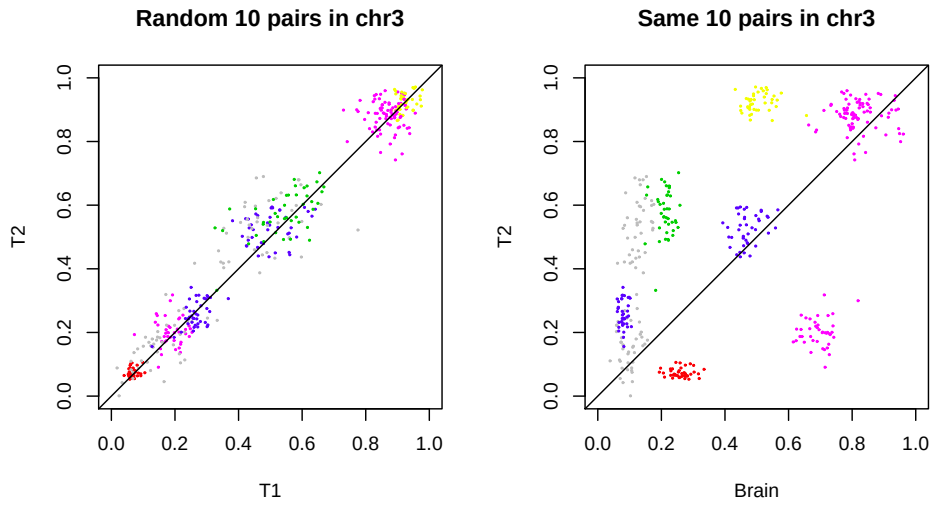




DNA methylation at random CpG sites



Pair plot of DNA methylation at random CpG sites



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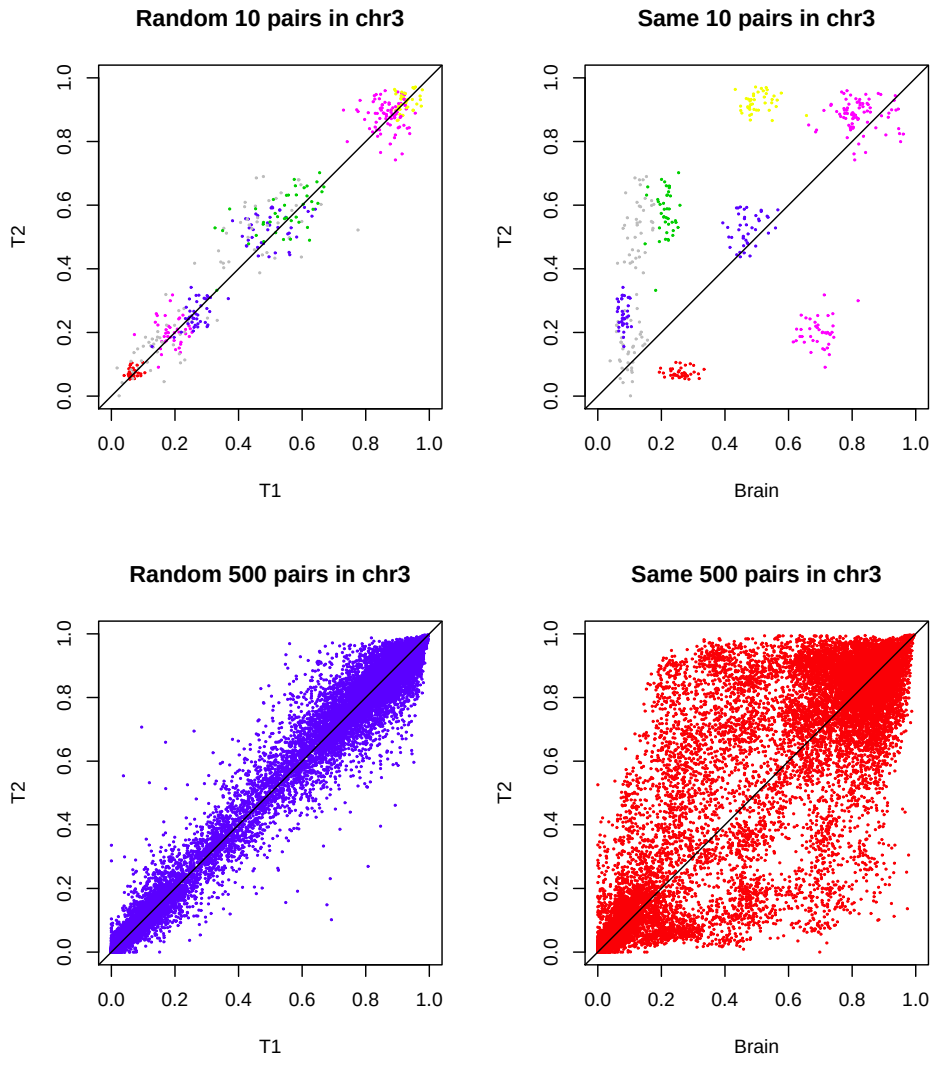
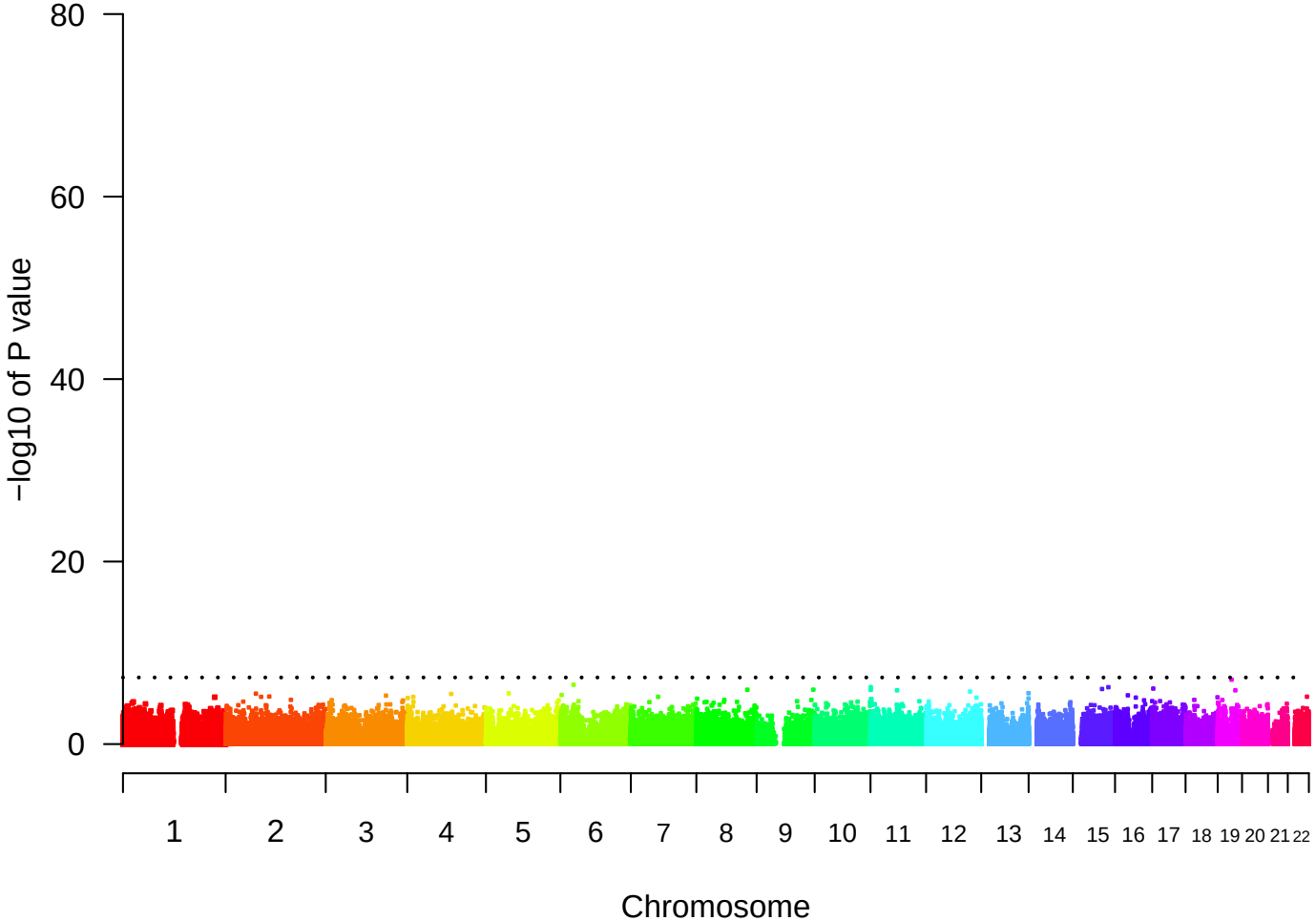
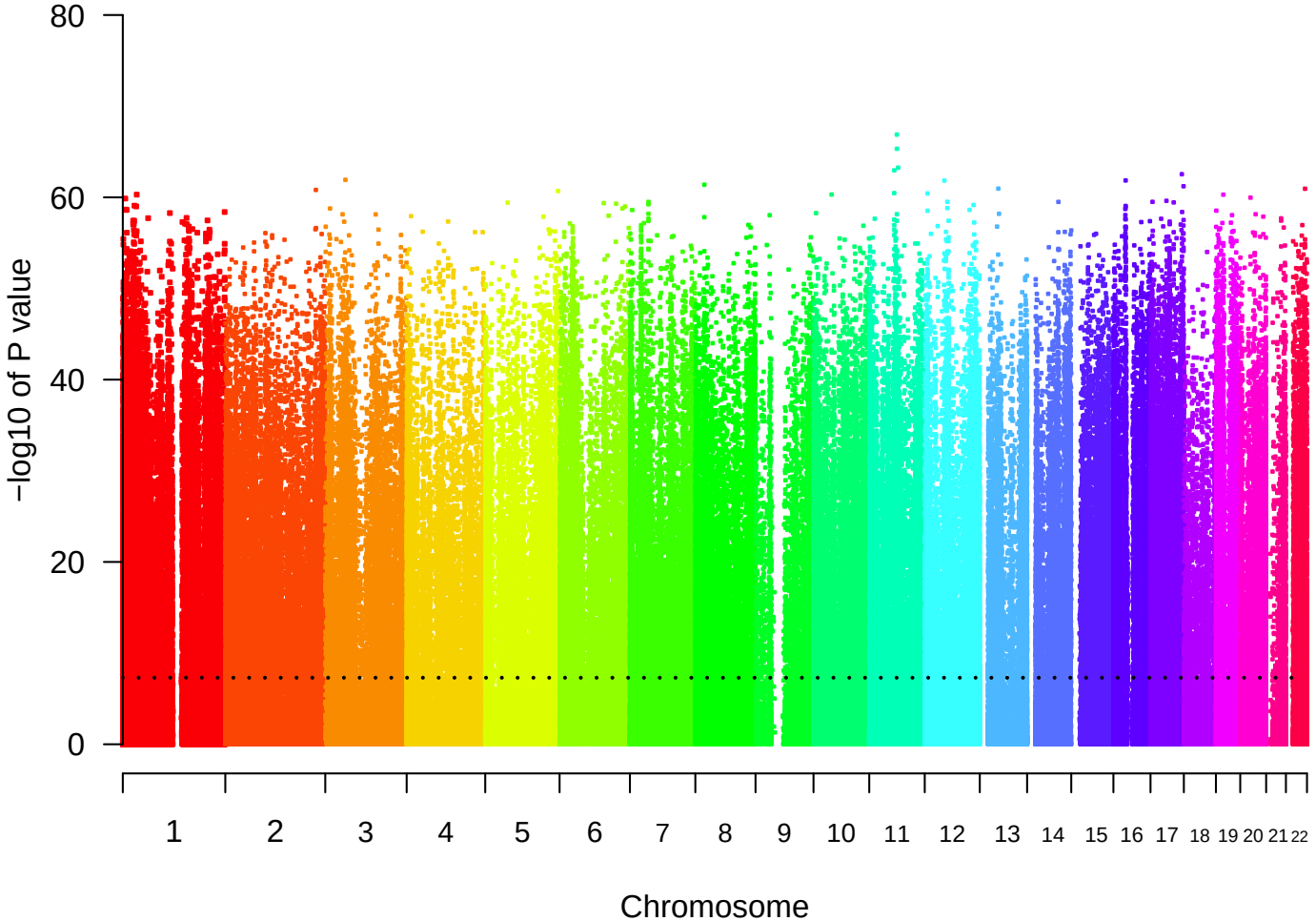


Difference between T1 and T2



Difference between T2 and brain



Top CpGs associated with AD

CpG	CHR	Est	p	Nearby genes
cg11724984	12	3.02	4.76×10^{-9}	RNF34, KDM2B
cg23968456	10	4.97	3.97×10^{-10}	CDH23, C10orf105, C10orf54
cg15821544	1	3.52	1.17×10^{-7}	SLC2A1, FLJ32224
cg16733298	16	2.75	5.24×10^{-8}	COQ7, ITPRIPL2
cg22962123	7	1.7	1.12×10^{-7}	HOXA1, HOTAIRM1, HOXA2, AK291164, HOXA3, ...
cg13076843	17	2.35	1.68×10^{-9}	UBE2O, AANAT, RHBDF2, AX747521, CYGB, PRCD
cg25594100	7	3.15	2.54×10^{-11}	FOXK1, AP5Z1 (KIAA0415), RADIL
cg00621289	21	3.5	6.48×10^{-8}	PCNT, DIP2A
cg19803550	17	4.36	1.04×10^{-8}	PRPF8, TLCD2, MIR22HG, AF070569, MIR22, WDR81, ...
cg03169557	16	4.86	3.99×10^{-10}	ANKRD11, SPG7, SNORD68, RPL13, CPNE7
cg05066959	8	2.69	7.13×10^{-14}	AGPAT6, NKX6-3, JA429246, ANK1
cg05810363	17	2.95	3.68×10^{-10}	UBE2O, AANAT, RHBDF2, AX747521, CYGB, PRCD
cg22883290	2	4.41	3.73×10^{-8}	BIN1
cg02308560	19	2.19	3.06×10^{-8}	CNN2, ABCA7, HMHA1, POLR2E, GPX4, SBNO2

(De Jager et al. 2014 *Nat Neurosci* Table 1)

Comparison of associations with neuritic plaques between blood and brain

CpG	Est (brain)	*p* (brain)	Est (T1)	*p* (T1)	Est (T2)	*p* (T2)
cg11724984	4.48421	0.008	-4.47558	0.761	-37.32927	0.027
cg23968456	8.92299	0.014	0.29185	0.985	3.86053	0.826
cg15821544	6.05472	0.025	-18.28297	0.023	0.62902	0.931
cg16733298	4.53274	0.006	5.07275	0.378	1.84116	0.708
cg22962123	2.43252	0.036	12.06577	0.144	-6.71269	0.165
cg13076843	2.66407	0.033	-3.62692	0.599	-7.97847	0.233
cg25594100	5.98322	0.001	-14.31339	0.111	-2.78358	0.778
cg00621289	7.65410	0.003	2.54079	0.504	-9.64311	0.048
cg19803550	7.79731	0.002	3.19687	0.727	2.19308	0.865
cg03169557	7.01246	0.006	-5.84686	0.369	-25.30343	0.180
cg05066959	2.35733	0.091	-4.72639	0.062	0.10942	0.969
cg05810363	3.50167	0.052	-11.12024	0.487	-13.72232	0.576
cg22883290	8.23246	0.006	-11.02340	0.387	4.79474	0.678
cg02308560	0.89543	0.493	1.24928	0.606	2.38878	0.380

Conclusions

- Global features of DNA methylation are largely conserved between blood and brain;
- Concordance between bloods, and more diffuse between blood and brain;
- Approximately half of the CpG sites differ between blood and brain; a majority show lower methylation level in brain.
- Brain methylation association with AD pathology are not replicated in blood.

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