SUPPLEMENTAL DATA

Table S1. Sample characteristics

	Mean (SD) or proportions
SYS adolescents	
Sample size (n)	132
Males/females	0.50/0.50
Age (years)	15.6 (1.4)
SYS parents	
Sample size (n)	278
Males/females	0.50/0.50
Age (years)	43.3 (5.0)
IMAGEN	
Sample size (n)	639
Males/females	0.47/0.53
Age (years)	15.0 (0)
OFCCR	
Sample size (n)	1,747
Males/females	0.49/0.51
Age (years)	63.7 (8.2)
Cases/controls	0.51/0.49

Table S2. Polymorphic CpGs loading into PC1 and their respective *local* meQTLs (SNP ID, position and minor allele frequency [MAF])

CpG ID	CpG position	SNP ID	SNP position	MAF (SYS adolescents)
cg17369694	32,485,396	rs112749594	32,485,397	0.25
cg01341801	32,489,203	rs114828939	32,489,204	0.21
cg23365293	32,489,984	rs111522006	32,489,985	0.14
cg08265274	32,490,444	rs145638935	32,490,444	0.05
cg22627029	32,520,615	rs113201078	32,520,615	0.10
cg25140213	32,522,683	rs35373206	32,522,683	0.10
cg10995422	32,522,872	rs67218022	32,522,872	0.29
cg24638099	32,526,027	rs150543195	32,526,028	0.12
cg11752699	32,526,669	rs34195497	32,526,670	0.14
cg26590106	32,548,321	rs9269762	32,548,321	0.17
cg11404906	32,551,749	NA	NA	NA
cg09139047	32,552,042	rs183889763	32,552,043	0.05
cg15602423	32,552,095	rs188617679	32,552,096	0.06
cg00211215	32,552,246	NA	NA	NA
cg09949906	32,552,350	rs28724124	32,552,350	0.09
cg22933800	32,605,704	NA	NA	NA
cg24470466	32,608,858	rs4455710	32,608,858	0.37
cg11784298	32,610,971	rs1130158	32,610,972	0.47
cg14323910	32,628,305	NA	NA	NA
cg10180404	32,632,334	rs143732234	32,632,335	0.25
cg10180404	32,632,334	rs9274341	32,632,336	0.23
cg21493951	32,632,338	NA	NA	NA
cg18572898	32,712,103	rs114448843	32,712,104	0.40
cg07389699	32,728,786	rs116328271	32,728,787	0.38
cg24080129	32,797,488	rs4148874	32,797,488	0.32

Table S3. Summary of HaploReg transcription factor position weight matrix (PWM) analysis of rs4959030

PWM	Strand	Ref	Alt	Ref: TAGGCCCAGAATTCTGCATGGTGGGTAGG**A**GCTGTGGCTTGTCTTGAAGCTGGATGTGC Alt: TAGGCCCAGAATTCTGCATGGTGGGTAGG**G**GCTGTGGCTTGTCTTGAAGCTGGATGTGC
BCL_disc7	-	15.2	3.7	RGGMGCTGT
BDP1_disc3	+	12.4	12.8	SNNNDRGSWSDGRS
CCNT2_disc2	-	9.2	12.5	RGGGBHGGGG
Ets_disc5	+	11.1	7.8	GGAGTTGT
Evi-1_5	-	11.9	13.1	BBYTGTGGYYW
PU.1_disc3	+	-0.4	11.6	RGVVVNDGSVDSDS
RREB-1_1	-	-6.5	5.4	KKKKKKKKKTGGGK
Sin3Ak-20_disc4	-	16.7	5.1	MGSWGCTGT

Shown are the PWMs that match a collection of PWMs collected by HaploReg. PWMs that matched either the reference (Ref) or alternative (Alt) at a given threshold and overlapped the sequence variant are shown (see HaploReg for details). The log-odds (LOD) score for each match is shown for the Ref (A) Alt (G) allele. IUPAC abbreviations for PWMs are shown at aligned positions of rs4959030. Note the hg19 Ref allele is the minor allele.

Table S4. LD between the meQTL (rs4959030) and 18 previously identified loci of disease in GWAS of European ancestry (only loci with r^2>0.2 within 32.18-32.67Mb on chromosome 6 are shown)

SNP ID	LD (r^2) with rs4959030	Disease/Trait	P	PubMed ID	Journal
rs3132946	0.58	Interstitial lung disease	8.00E-06	23583980	*Nat Genet*
rs3129934	**0.59**	**Multiple sclerosis**	**7.00E-16**	**22457343**	***Mult Scler***
rs3129934	**0.59**	**Multiple sclerosis**	**9.00E-11**	**18941528**	***PLoS One***
rs4959027	0.42	Pubertal anthropometrics	9.00E-07	23449627	*Hum Mol Genet*
rs3129871	**0.20**	**Multiple sclerosis**	**6.00E-15**	**23472185**	***PLoS One***
rs3129871	**0.20**	**Multiple sclerosis**	**1.00E-16**	**23472185**	***PLoS One***
rs3135388	**0.80**	**Multiple sclerosis**	**4.00E-225**	**19525953**	***Nat Genet***
rs3135388	**0.80**	**Multiple sclerosis**	**9.00E-81**	**17660530**	***N Engl J Med***
rs2227139	0.31	Hematological parameters	1.00E-07	19820697	*Nat Genet*
rs3129889	**0.80**	**Multiple sclerosis**	**1.00E-206**	**22190364**	***Ann Neurol***
rs6903608	0.30	Hodgkin's lymphoma	5.00E-27	24149102	*Nat Commun*
rs6903608	0.30	Hodgkin's lymphoma	3.00E-50	21037568	*Nat Genet*
rs3828840	**0.26**	**Multiple sclerosis**	**5.00E-15**	**23472185**	***PLoS One***
rs9271192	0.35	Alzheimer's disease	3.00E-12	24162737	*Nat Genet*
rs9271348	0.27	Rheumatoid arthritis	5.00E-07	24532677	*Ann Rheum Dis*
rs9271366	**0.76**	**Multiple sclerosis**	**4.00E-17**	**20598377**	***J Neuroimmunol***
rs9271366	**0.76**	**Multiple sclerosis**	**7.00E-184**	**19525955**	***Nat Genet***
rs9271640	**0.38**	**Multiple sclerosis**	**2.00E-20**	**23472185**	***PLoS One***
rs9274407	0.49	Drug-induced liver injury	5.00E-14	21570397	*Gastroenterology*
rs3129720	**0.48**	**Multiple sclerosis**	**5.00E-15**	**23472185**	***PLoS One***
rs3129720	0.48	Hypothyroidism	5.00E-07	22493691	*PLoS One*
rs6457617	0.20	Systemic sclerosis	2.00E-37	21750679	*PLoS Genet*
rs6457617	0.20	Systemic sclerosis	4.00E-17	20383147	*Nat Genet*
rs6457617	0.20	Rheumatoid arthritis	1.00E-09	18668548	*Arthritis Rheum*
rs6457617	0.20	Rheumatoid arthritis	5.00E-75	17554300	*Nature*
rs6457620	0.20	Height	2.00E-16	20881960	*Nature*
rs6457620	0.20	Rheumatoid arthritis	4.00E-186	18794853	*Nat Genet*
rs2647012	0.31	Follicular lymphoma	2.00E-21	21533074	*PLoS Genet*
rs2647012	0.31	Systemic lupus erythematosus	8.00E-06	21408207	*PLoS Genet*

Figure S1: Principal component analysis of unadjusted (A) and adjusted (B) DNAm-β values of 1,000 most variable CpGs in the genome. Panel A shows the two distinctive clusters (indicated by red and black dots) revealed by the original PCA of unadjusted DNAm-β values. Panel B suggests that this clustering pattern is not fully explained by age, sex, batch and blood cell proportions.

Figure S2: Heritability (h^2) of DNA methylation and the relative contributions (r^2) of the *long-range* and *local* meQTLs to methylation of CpGs within the studied 300-kb genomic region. The heritability estimates (h^2), obtained using the combined sample of SYS adolescents and their parents, are indicated by green lines. The relative contributions (r^2) of the *long-range* and respective *local* meQTLs are indicated by purple lines and yellow lines with stars, respectively. Grey triangles indicate the combined contribution of the *long-range* and respective *local* meQTLs at each assessed CpG. The top panel includes the 25 highly variable CpGs loading into PC1 (including 19 polymorphic CpGs). The middle panel includes a total of 456 CpGs (including 85 polymorphic CpGs). The bottom panel includes the same 456 CpGs, which are equally spaced for better visualization.

Figure S3: The relative contributions of *local* meQTLs to methylation of CpGs within the studied genomic region. The contributions are shown as proportions of 'variance explained' (r^2) by *local* meQTL (independently of the *long-range* meQTL, yellow lines with stars). Grey triangles indicate the combined contribution of the *long-range* and respective *local* meQTLs at each assessed CpG. The top panel includes the 25 highly variable CpGs loading into PC1 (including 19 polymorphic CpGs). The middle panel includes a total of 456 CpGs (including 85 polymorphic CpGs). The bottom panel includes a total 5,663 CpGs (including 273 polymorphic CpGs) located within the region of high linkage disequilibrium with meQTL (as shown in Figure 1).

Figure S4: Inter- and intra-species analysis of the *long-range* meQTL (rs4959030). (A) The region surrounding rs495930 is primate specific and the hg19 reference sequence for rs4959030 is the minor allele A. The multiple sequence alignments were taken from the Vertebrate Multiz Alignment (100 species) from the UCSC genome browser. **(B)** The hg19 reference allele for rs4959030 (minor allele A) disrupts a PU.1 motif (PU.1_disc3). The PU.1_disc3 (also known as SPI1_disc3) motif was obtained from Kheradpour and Kellis (66) and plotted as a sequence logo using RSAT (67).

Figure S5: Association of the *long-range* meQTL (rs4959030) with fractional anisotropy assessed with diffusion tensor imaging of the human brain. A subset of SYS parents with relevant brain imaging data (n=309) was studied. The association was tested while adjusting for sex and age.

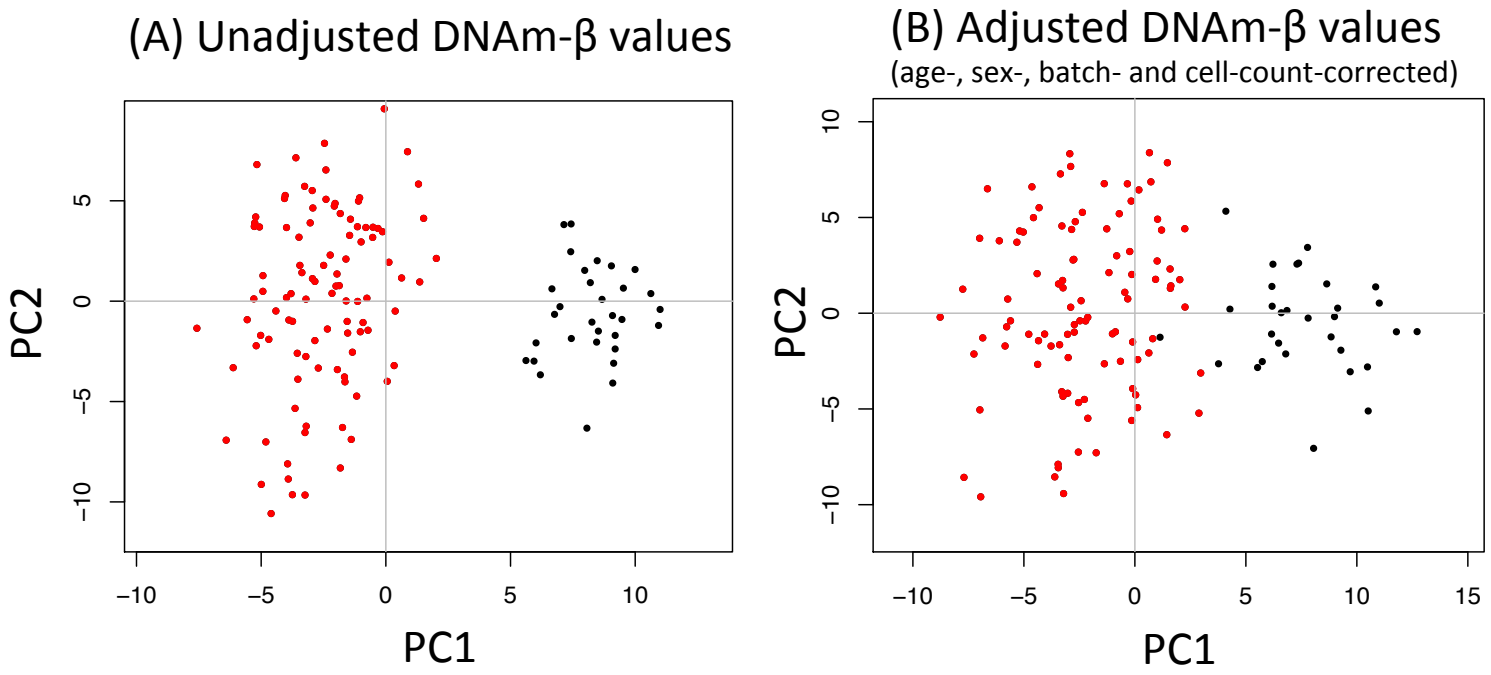

Figure S1. Principal component analysis of unadjusted (A) and adjusted and (B) DNAm-β values of 1,000 most variable CpGs in the genome.

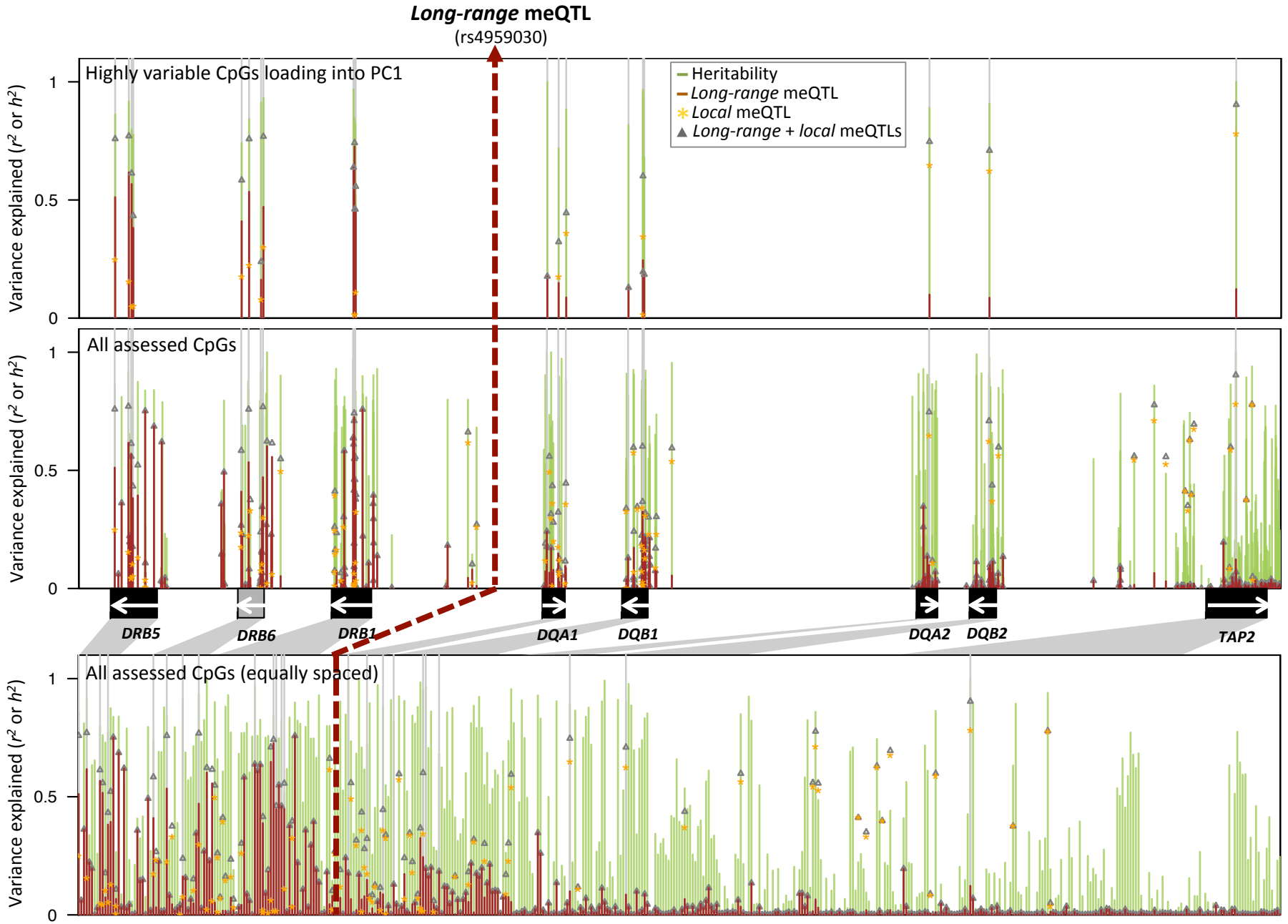

Figure S2. Heritability (h^2) of DNA methylation and the relative contributions (r^2) of the *long-range* and *local* meQTLs to methylation of CpGs within the studied 300-kb genomic region.

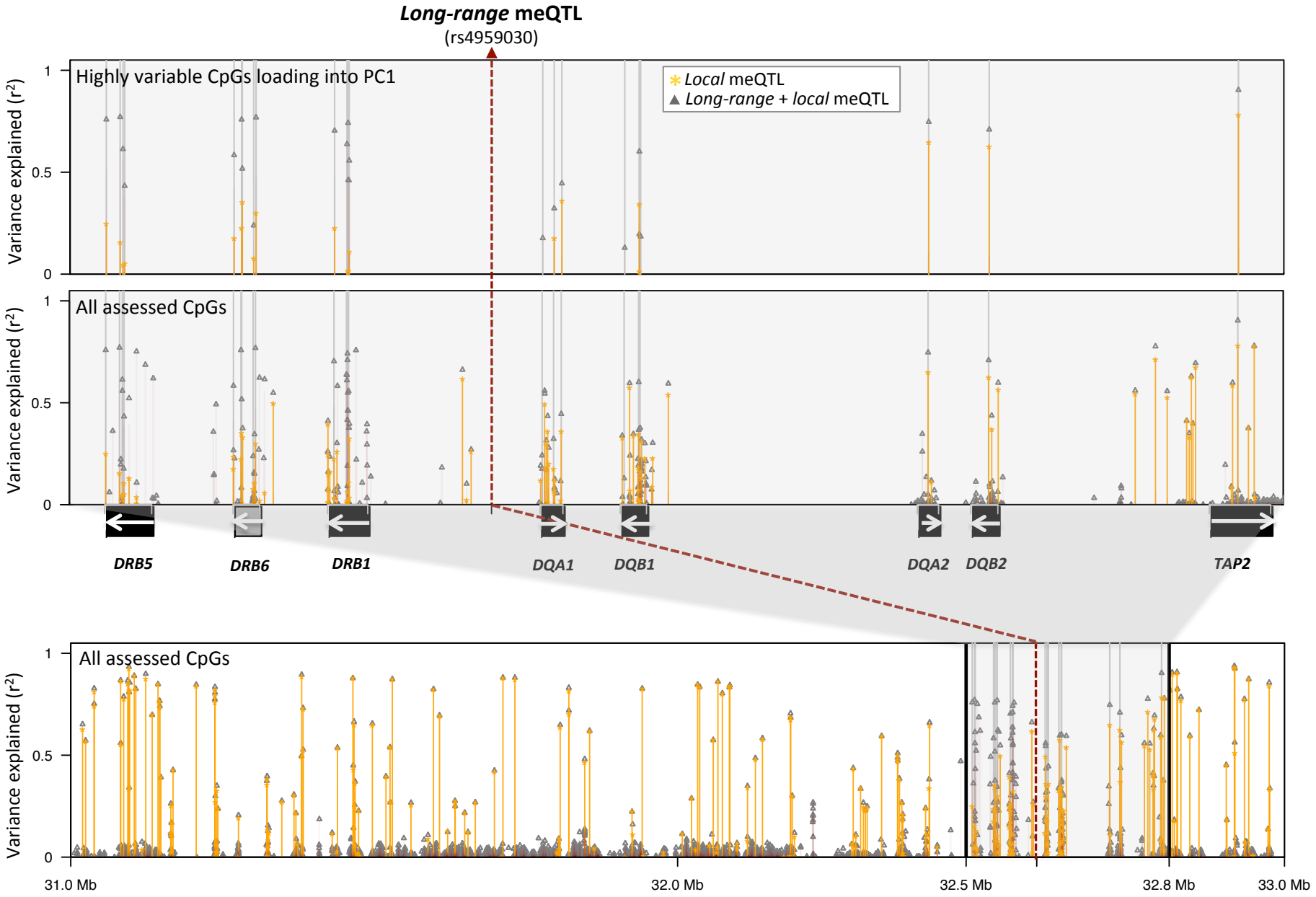

Figure S3. The relative contribution of *local* meQTLs to methylation of CpGs within the studied genomic region.

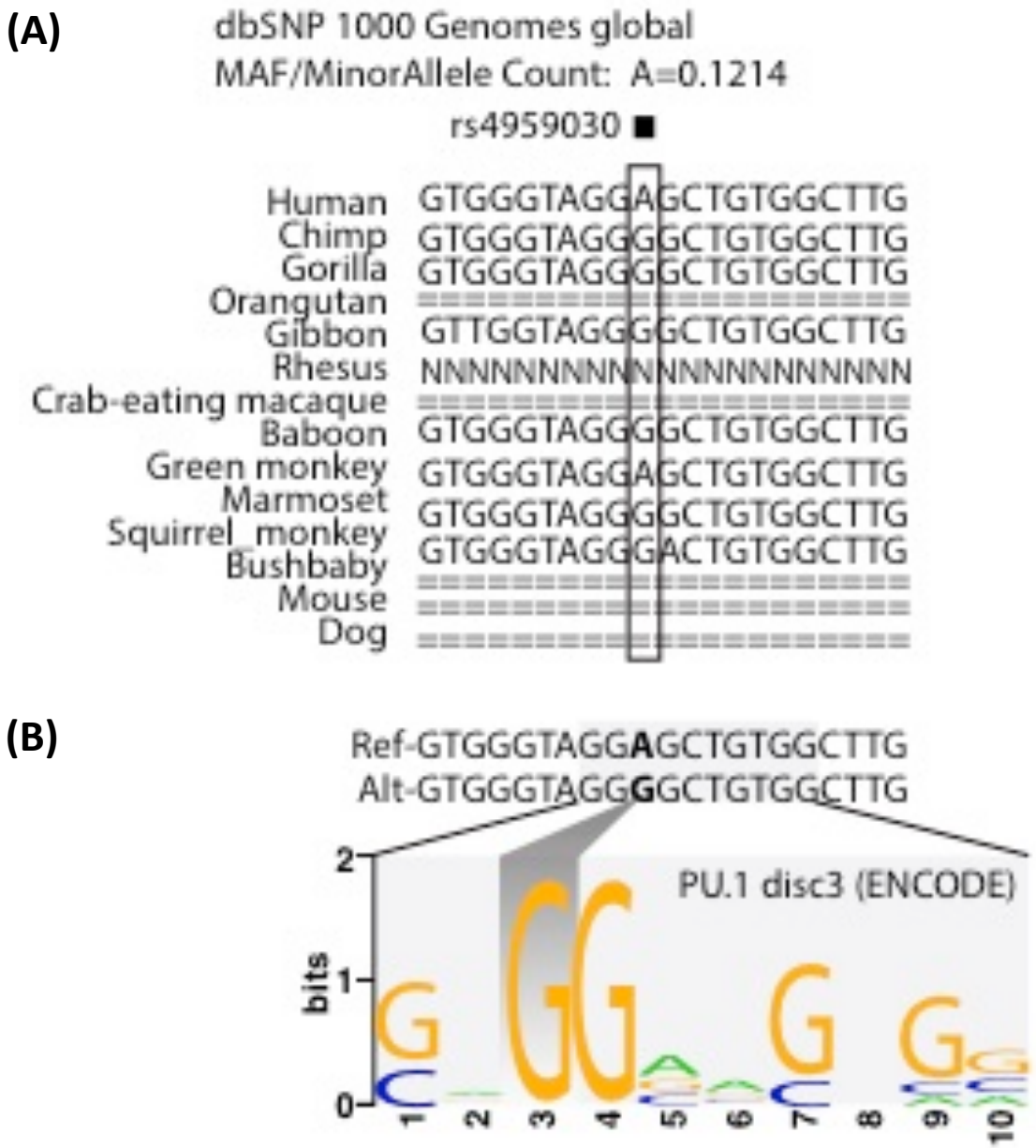

Figure S4. Inter- and intra-species analysis of the *long-range* meQTL (rs4959030).

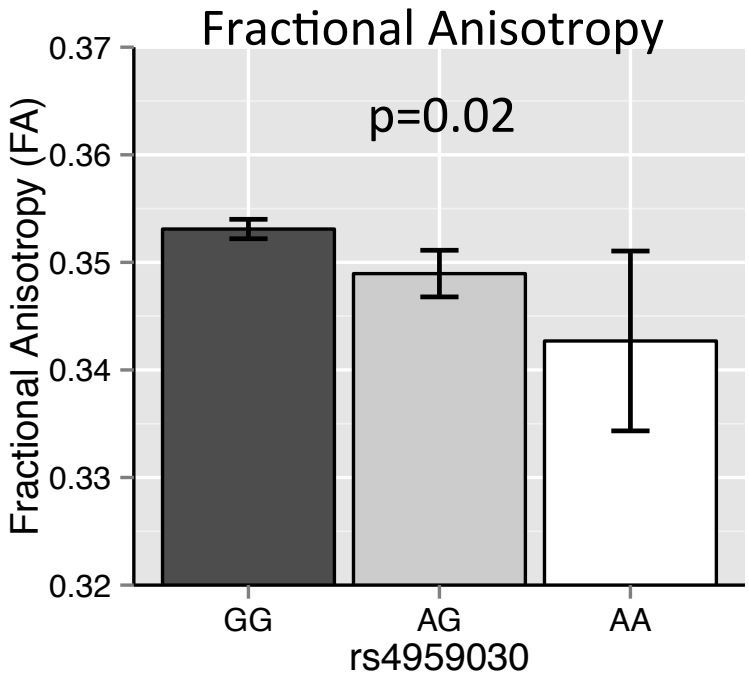

Figure S5. Association of the *long-range* meQTL (rs4959030) with fractional anisotropy assessed with diffusion tensor imaging of the human brain.

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