Table 1. Control Probes on the Illumina 450K methylation array.

Category	Description	No. of Types	No. of Probes
Bisulfite Conversion	Methylation at a site known to be methylated	3	10
Normalisation	Randomly permutated bisulphite-converted sequences containing no CpGs; Determines system background	4	186
Staining	Efficiency and sensitivity of staining step	2	2
Extension	Extension efficiency of A, T, C, and G nucleotides from a hairpin probe	4	4
Hybridisation	Hybridisation efficiency using synthetic targets instead of amplified DNA	3	3
Target Removal	Efficiency of stripping step after extension reaction	1	2
Specificity	Methylation at non-polymorphic T sites	3	9
Non-polymorphic	Methylation at a base in a non-polymorphic region of the genome	4	4

Table 2: Genomic Inflation Factor λ under the null hypothesis by permutation testing, using different levels of adjustment.

	Median	2.5 Percentile	97.5 Percentile
no adjustment	0.91	0.58	2.87
QN	0.98	0.80	1.44
+ Control Probe PCs	0.96	0.84	1.46
+ Gender, Age	0.96	0.84	1.47
+ WBC_{tot} + WBC_{est}	1.00	0.96	1.09
+ PC 1-5	1.00	0.97	1.05

Table 3. Simulations show significant performance improvements for each stage of the analysis pipeline (paired Wilcoxon rank test).

	% of spiked markers in top 100		
	Median	**2nd Decile**	**9th Decile**
no adjustment	46%	1%	97%
QN	66%	5%	98%
+ Control Probe PCs	71%	6%	98%
+ Gender, Age	71%	6%	98%
+ WBC_{tot} + WBC_{est}	75%	5%	99%
+ PC 1-5	76%	6%	99%

Table 4. Baseline characteristics of South Asian incident T2D cases and controls in the epigenome-wide association study. Results are presented as mean (SD) or as % (N).

	Incident T2D	**Controls**	**P**
N	1,074	1,590	
Follow-up (yrs)	8.6 (1.7)	8.4 (1.7)	0.94
Age (yrs)	52.5 (10.2)	49.9 (9.8)	<0.001
Sex (M)	67.3% (722)	68.2% (1,083)	0.61
Impaired fasting glucose	18.9% (207)	3.4% (55)	<0.001
Fasting glucose (mmol/L)	5.49 (0.59)	5.05 (0.47)	<0.001
HbA1c (%)	5.77 (0.49)	5.37 (0.48)	<0.001
Insulin (IU/L)	15.5 (10.9)	10.7 (9.2)	<0.001
Body mass index (kg/m^2)	28.9 (4.6)	26.7 (3.9)	<0.001
Waist circumference (cm)	101.0 (11.5)	94.9 (10.3)	<0.001
Waist-hip ratio	0.97 (0.07	0.94 (0.07)	<0.001

Table 5. Association of methylation markers with future T2D. Results are presented as relative risk for T2D [95% confidence interval] associated with a 1SD increase in respective methylation marker in the discovery phase (1,074 Indian Asians with incident T2D and 1,590 controls), in replication testing amongst 1,141 Europeans (377 with incident T2D), and in combined analysis. P_{het} is for heterogeneity of effect between discovery and replication.

Marker	Discovery	P	Replication	P	Combined	P	P_{het}
Marker 1	0.68 [0.62, 0.75]	1.0×10^{-13}	0.70 [0.60, 0.83]	2.5×10^{-5}	0.68 [0.63, 0.75]	1.5×10^{-18}	0.98
Marker 2	0.77 [0.70, 0.85]	9.3×10^{-8}	0.94 [0.82, 1.07]	0.32	0.83 [0.77, 0.89]	4.8×10^{-7}	0.04
Marker 3	0.68 [0.60, 0.78]	1.4×10^{-8}	0.98 [0.87, 1.10]	0.71	0.84 [0.78, 0.92]	4.8×10^{-5}	0.004
Marker 4	1.40 [1.26, 1.57]	8.4×10^{-9}	1.19 [1.05, 1.34]	5.4×10^{-3}	1.30 [1.20, 1.41]	3.0×10^{-10}	0.07
Marker 5	0.73 [0.66, 0.81]	2.1×10^{-9}	0.80 [0.70, 0.92]	1.2×10^{-3}	0.75 [0.70, 0.82]	4.1×10^{-12}	0.48
Marker 6	0.78 [0.71, 0.85]	2.1×10^{-7}	0.81 [0.72, 0.93]	1.6×10^{-3}	0.79 [0.73, 0.85]	4.7×10^{-10}	0.76
Marker 7	1.44 [1.31, 1.58]	2.2×10^{-13}	1.31 [1.14, 1.50]	1.2×10^{-4}	1.40 [1.29, 1.51]	1.1×10^{-17}	0.32

Table 6. . Replication testing for association with prevalent T2D in Indian Asians. Results are expressed as OR (95%CI) per 1SD increase in methylation. P is the P-value in combined analysis.

Locus	Migrant	Non-Migrant	Combined	P
Marker 1	0.25 (0.19 to 0.33)	0.35 (0.30 to 0.42)	0.32 (0.28 to 0.37)	9.7E-55
Marker 4	1.53 (1.25 to 1.87)	1.50 (1.30 to 1.74)	1.51 (1.34 to 1.70)	9.8E-12
Marker 5	0.83 (0.68 to 1.00)	0.71 (0.62 to 0.80)	0.74 (0.67 to 0.83)	5.2E-08
Marker 6	0.93 (0.76 to 1.13)	0.75 (0.66 to 0.85)	0.80 (0.72 to 0.89)	6.8E-05
Marker 7	1.15 (0.97 to 1.36)	1.71 (1.46 to 2.01)	1.42 (1.26 to 1.60)	4.4E-09

Table 7. Summary of current knowledge for candidate genes at the identified loci.

Marker 1	- Key component of pancreatic beta cell biology, nutrient sensing, energy metabolism and regulation of cellular redox. - Downregulates GLUT1, the major transmembrane glucose transporter, thereby acting as a negative feedback loop to regulate glucose entry and mitochondrial oxidative stress. - May contribute to regulation of adiposity and energy expenditure through hypothalamic pathways.
Marker 4	- Master transcriptional regulator of hepatic lipogenesis, capable of inducing the entire complement of genes necessary for the synthesis of monounsaturated fatty acids. - Decreased in insulin-deficient states, such as fasting, but increased in feeding, obesity and insulin resistance.
Marker 5	- Encodes a phosphatase involved in the generation of inorganic phosphate for bone mineralization; highly expressed at sites of mineralization in bone and cartilage. - Not previously associated with obesity, insulin action or diabetes.
Marker 6	- Major negative regulator of insulin signaling, and implicated in the pathogenesis of obesity and associated metabolic abnormalities. - In mouse model, knockout mice are protected against obesity induced hyperinsulinemia and insulin resistance.
Marker 7	- Involved in macrophage cholesterol and phospholipid transport, and promotes cholesterol efflux to HDL. - Knockout mice have impaired glucose tolerance and insulin secretion with normal insulin sensitivity. - Expression downregulated in humans with diabetes and upregulated by the insulin sensitizing agents such as thiazolidenediones.

Table 8. Positive predictive value and sensitivity for prediction of T2D based on models comprising known risk factors with or without addition of methylation score. In each model, positive predictive value and sensitivity are calculated at the 90th centile of risk score in people without T2D.

	Positive Predictive Value		**Sensitivity for T2D**	
	Without methylation	*With methylation*	*Without methylation*	*With methylation*
Risk factors				
Age, Sex, Family history T2D, Physical activity	16.7%	21.2%	18.0%	25.0%
+ Body mass index, Waist-hip ratio	20.8%	25.0%	23.6%	30.2%
+ Glucose, HbA1c	33.6%	36.0%	48.8%	51.3%

Table 9. Association of DNA methylation with gene expression in peripheral blood amongst Indian Asians and Europeans.

	Peripheral Blood					
	LOLIPOP (SA; n=907)		**EGM (EUR; n=591)**		**KORA (EUR; n=703)**	
Marker	**Beta**	**P**	**Beta**	**P**	**Beta**	**P**
Marker 1	2.20	3.00E-02	0.12	8.40E-01	-0.03	3.40E-01
Marker 4	-3.73	2.00E-04	-1.58	8.80E-05	-0.15	3.80E-03
Marker 5	1.69	9.00E-02	3.29	2.00E-02	0.08	5.50E-01
Marker 6	-1.55	1.20E-01	2.58	1.90E-03	0.09	3.00E-02
Marker 7	-9.73	3.80E-21	-2.51	1.40E-06	-5.20	1.50E-20

Table 10. Characteristics of South Asians in the family study

	Mean	**SD**
Age (years)	38.0	15.3
Sex (male)	52.8%	
Coronary heart disease (%)	15.0%	
Type 2 Diabetes (%)	9.8%	
Glucose (mmol/L)	5.5	1.8
HbA1c (%)	5.1	1.1
Insulin (IU/L)	10.3	7.6
Body mass index (kg/m2)	25.5	4
Waist (cm)	88.0	35.2
Waist-hip ratio	0.88	0.37
Systolic BP (mmHg)	123.1	20.4
Diastolic BP (mmHg)	71.0	11.7
Cholesterol (mmol/L)	5.1	1.0
Triglycerides (mmol/L)	1.5	0.9
HDL cholesterol (mmol/L)	1.3	0.3

Figure 1. Correlation between duplicate measurements of methylation in each sample, using different approaches to data-normalisation. Subset QN: Subset Quantile Normalization; Raw: No normalisation; BMIQ: Beta MIxture Quantile dilation; PBC: Peak-Based Correction; Illumina: Illumina Control Probe Normalisation; SWAN: Subset Within-Array Normalisation; QN-I6: Quantile Normalisation of Intensity-values (6 categories). Methods are sorted based on the median correlation coefficient.

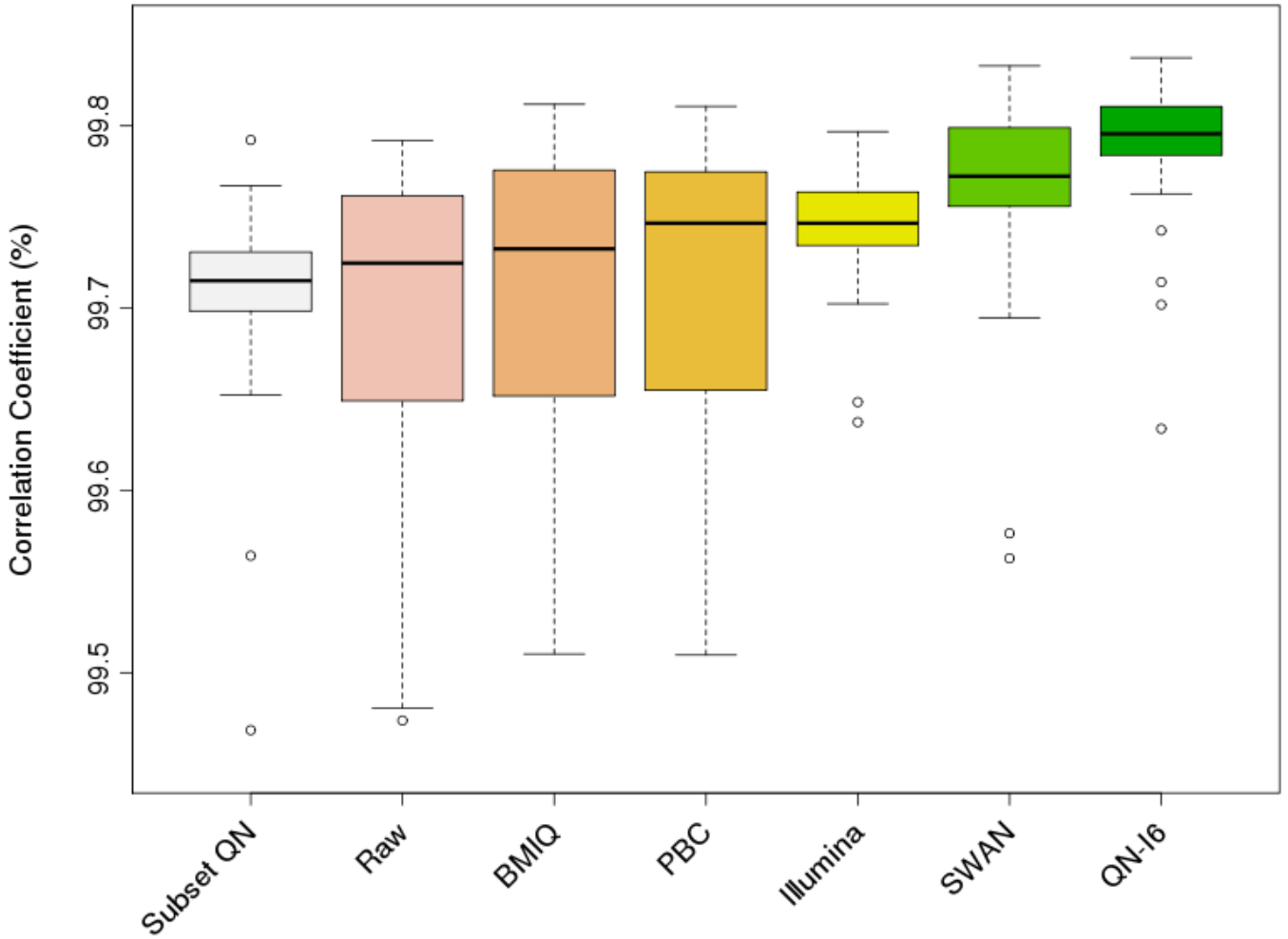


Figure 2. Simulation analysis comparing different approaches to data normalisation. For each normalisation method we increased ("spiked") beta-values of 100 randomly selected markers and determined the proportion of spiked markers that were ranked amongst the top 100. SWAN: Subset Within-Array Normalisation; Illumina: Illumina Control Probe Normalisation; Raw: No normalisation; BMIQ: Beta MIxture Quantile dilation; PBC: Peak-Based Correction; Subset QN: Subset Quantile Normalization; QN-I6: Quantile Normalisation of Intensity-values (6 categories). Methods in the figure legend are sorted based on the average percentage of top 100 spike-markers.

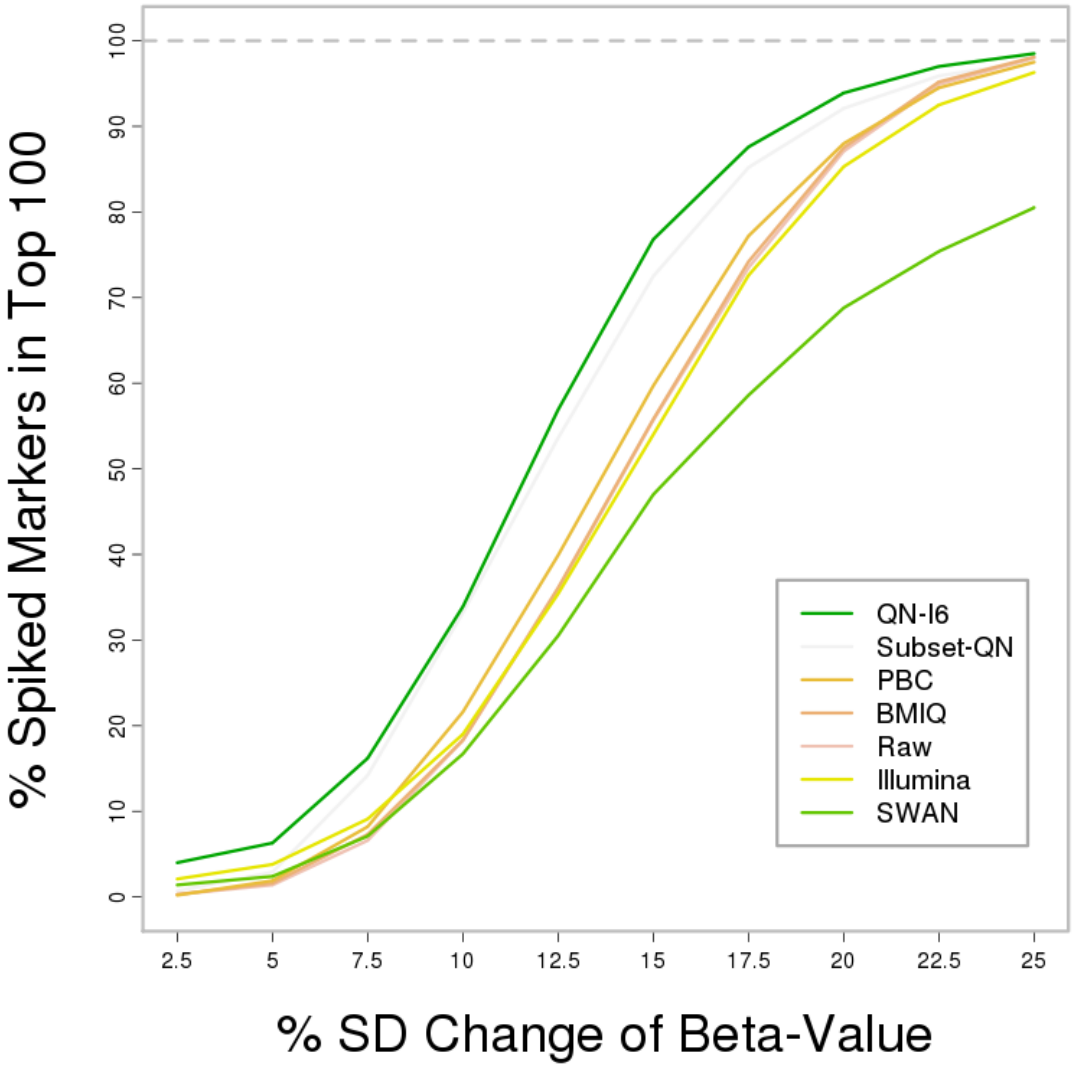


Figure 3. Correcting for statistical inflation due to technical biases. Quantile-Quantile (QQ) plot for the comparison of 36 samples measured in duplicate reveals high statistical inflation after quantile normalisation (λ_{QN}=2.11; green points) due to technical biases. Batch-correction based on control probes removes technical biases and statistical inflation (λ_{CP}=1.01; green points).

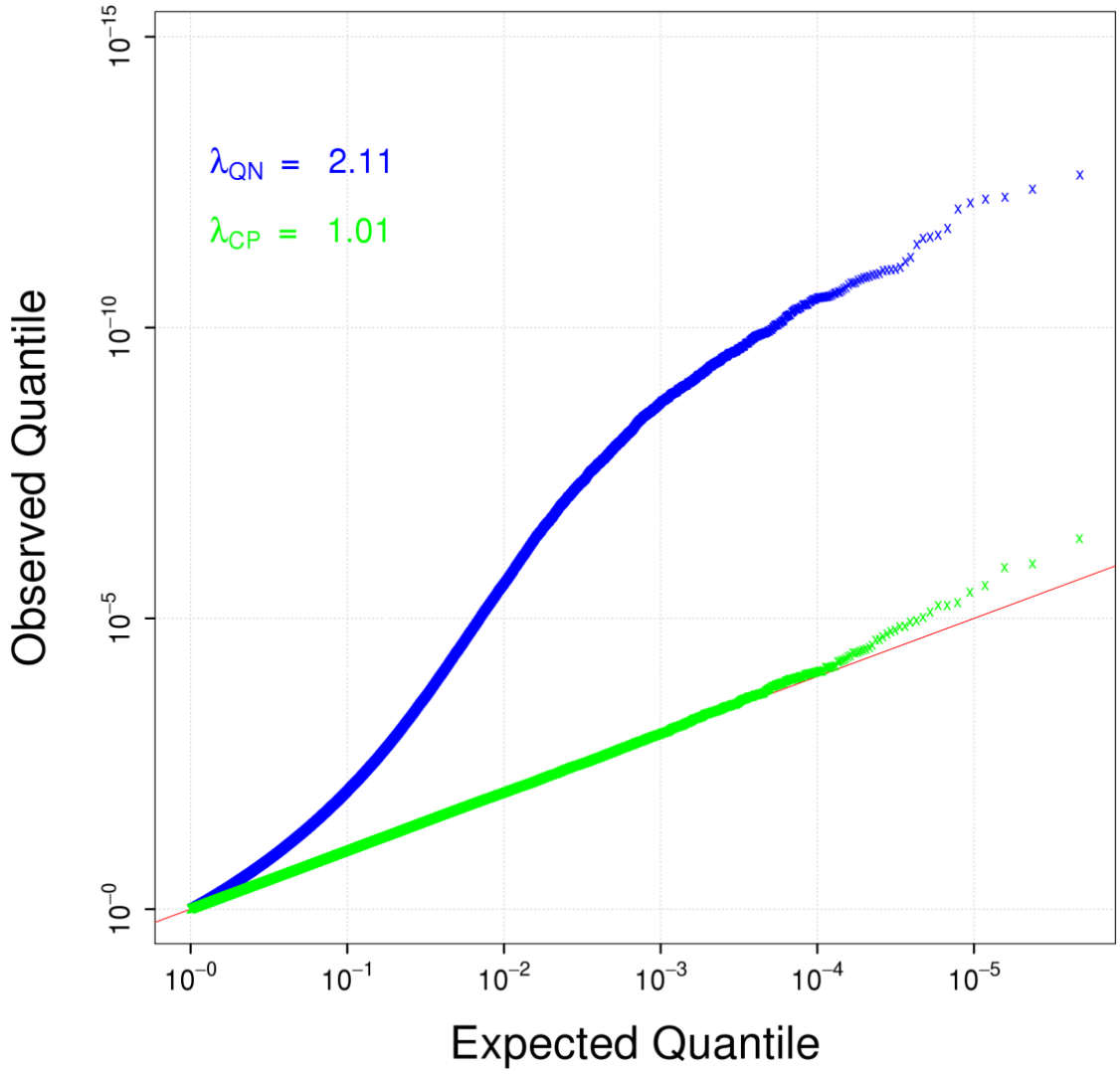


Figure 4. PCA of control probe intensities reveals strong correlations between Principal Components and technical factors in the population study.

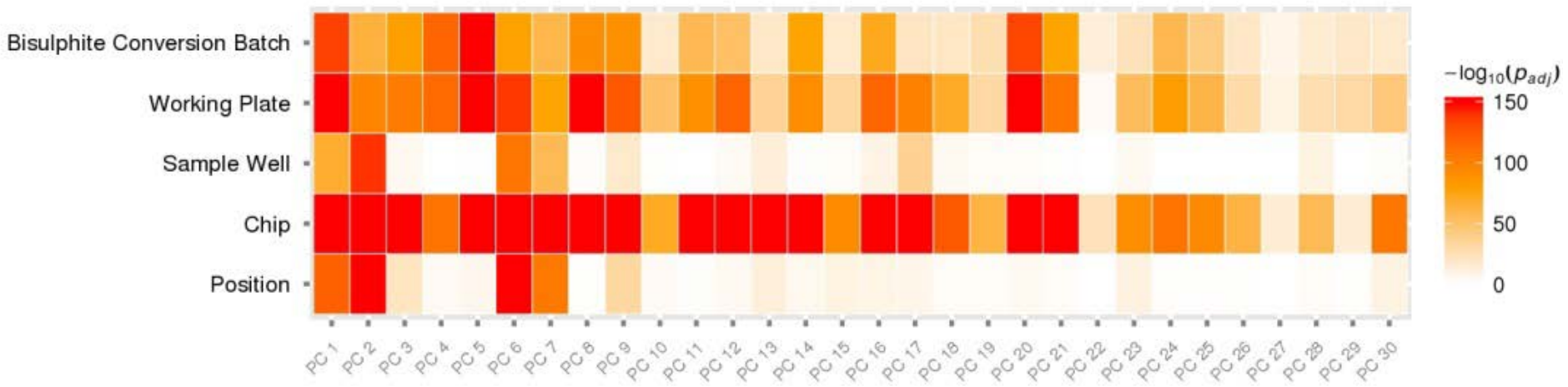


Figure 5. QQ plot showing results for the Epigenome-wide association study. Blue dots represent results for individual CpG sites for association with T2D. The red line represents the null hypothesis of no association; the grey shading provides the 95% confidence interval for the null hypothesis.

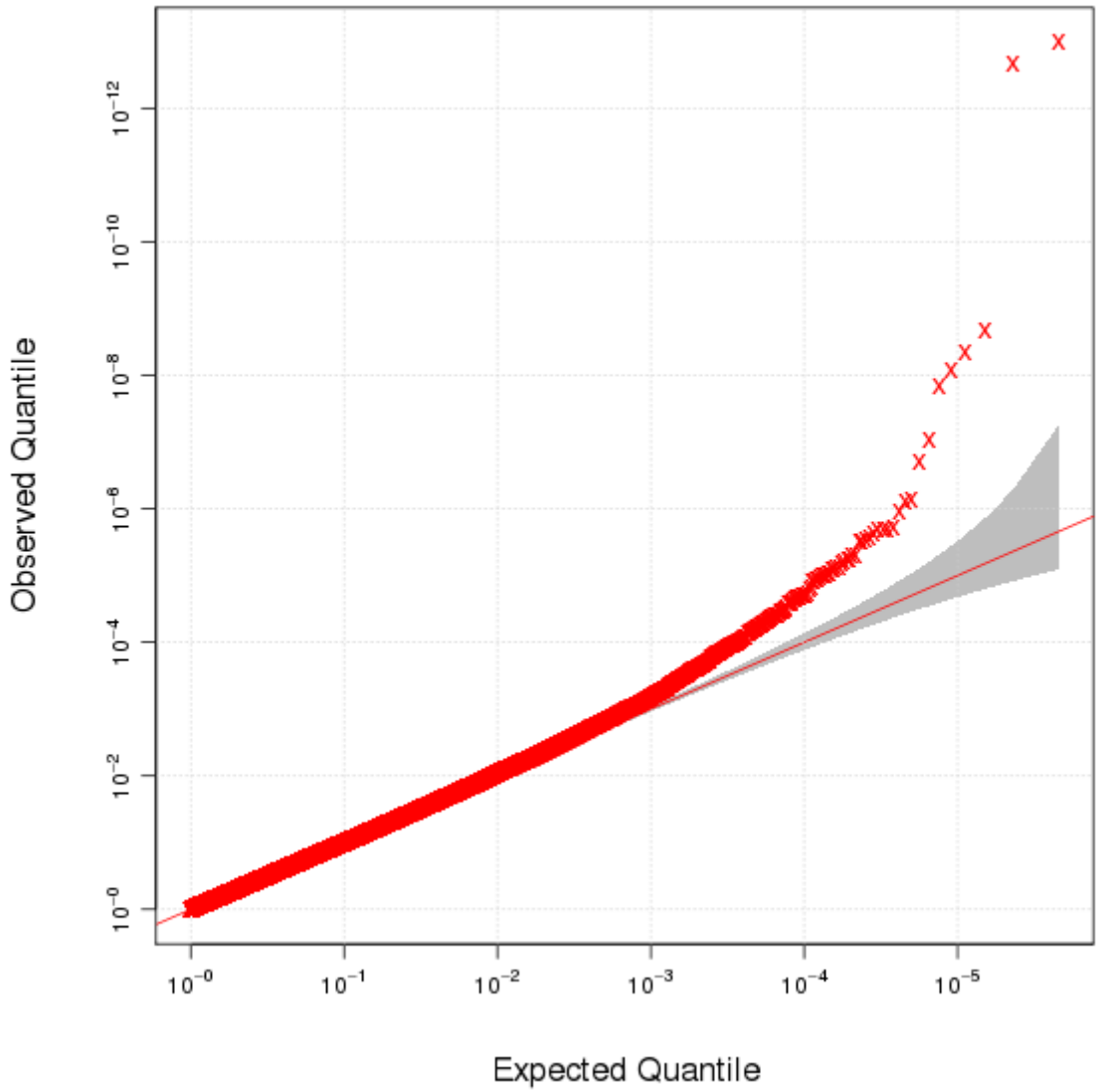


Figure 6. Manhattan plot for the Epigenome-wide association study

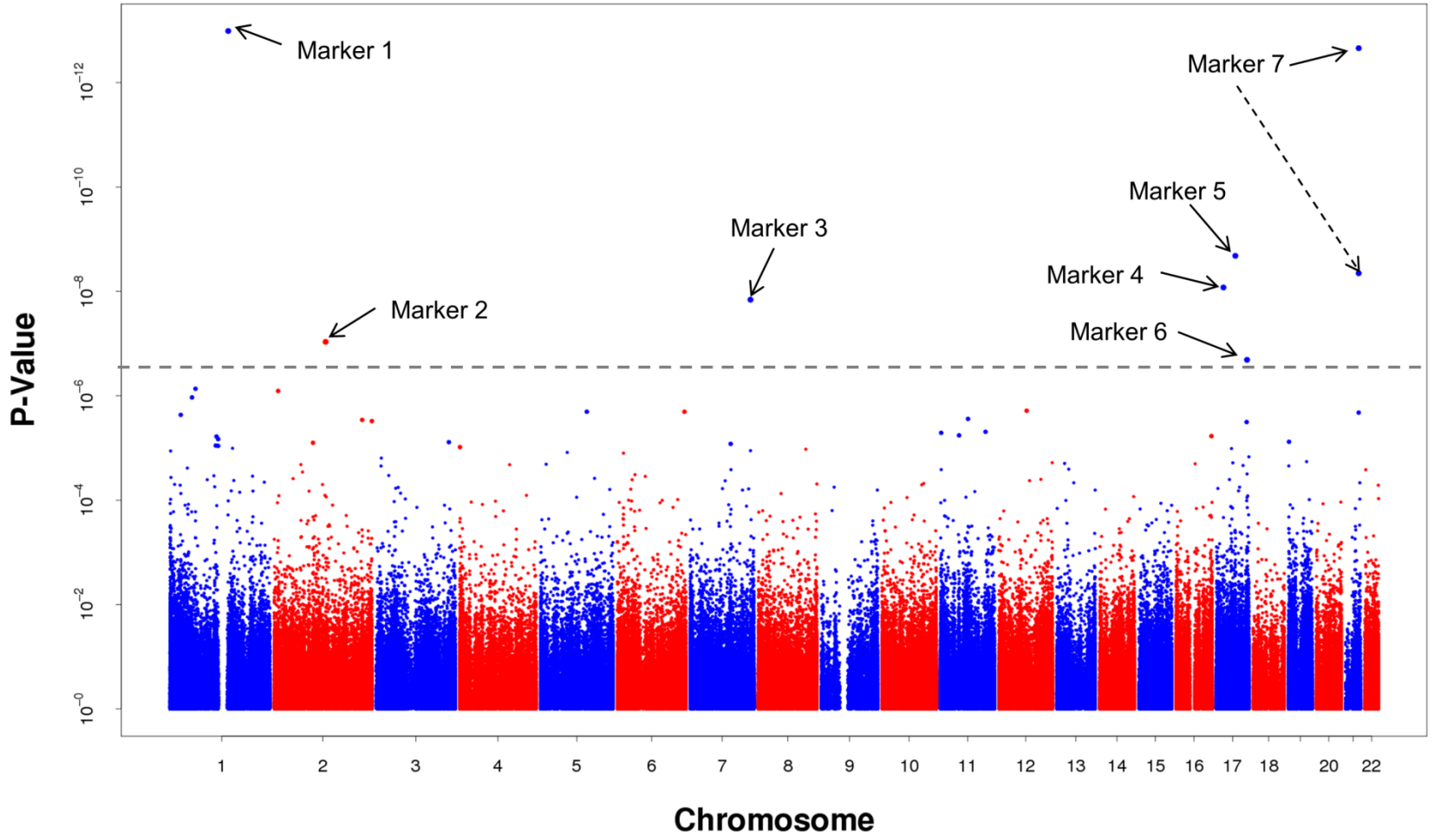


Figure 7. Relative risk of T2D (with 95% Confidence Interval) between top and bottom quartiles of methylation for replicated markers.

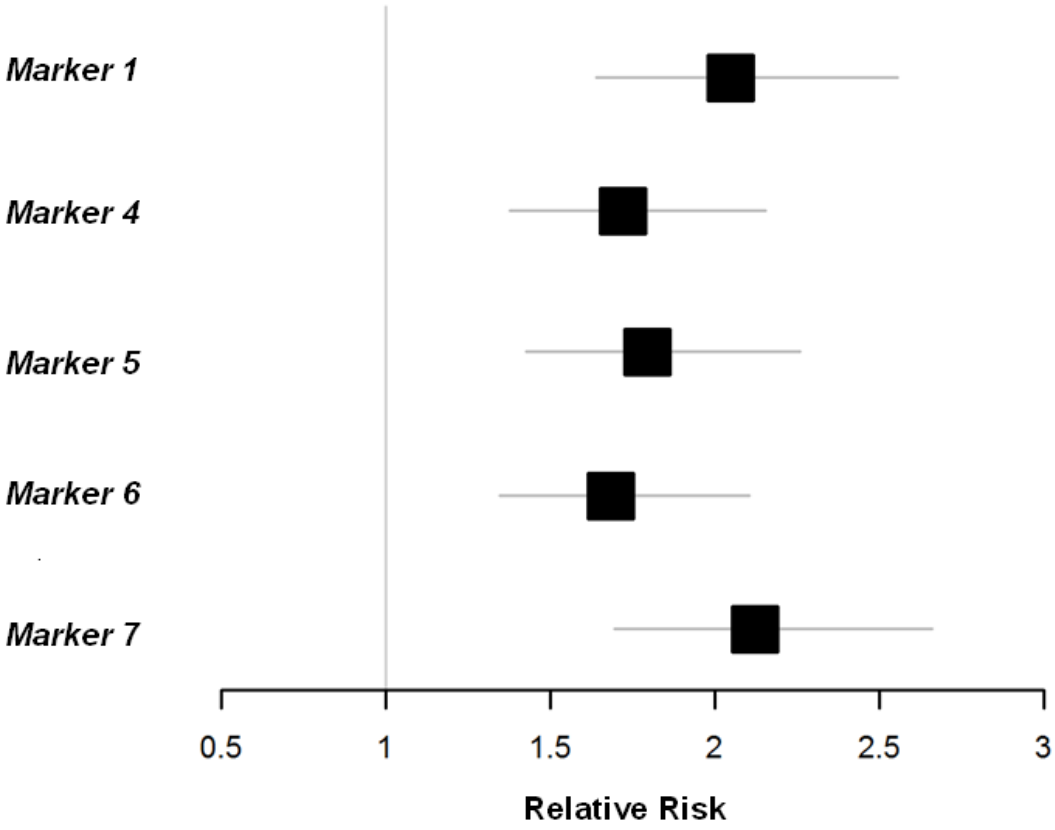


Figure 8. Incidence of T2D (8 year follow-up) by quartile of methylation score amongst normal weight (Body mass index [BMI] 18.5-24.9kg/m^2), overweight (BMI 25.0-29.9kg/m^2) and obese (BMI ≥30.0kg/m^2) Indian Asians with normoglycaemia (HbA1c<6% and fasting glucose<6mmol/l).

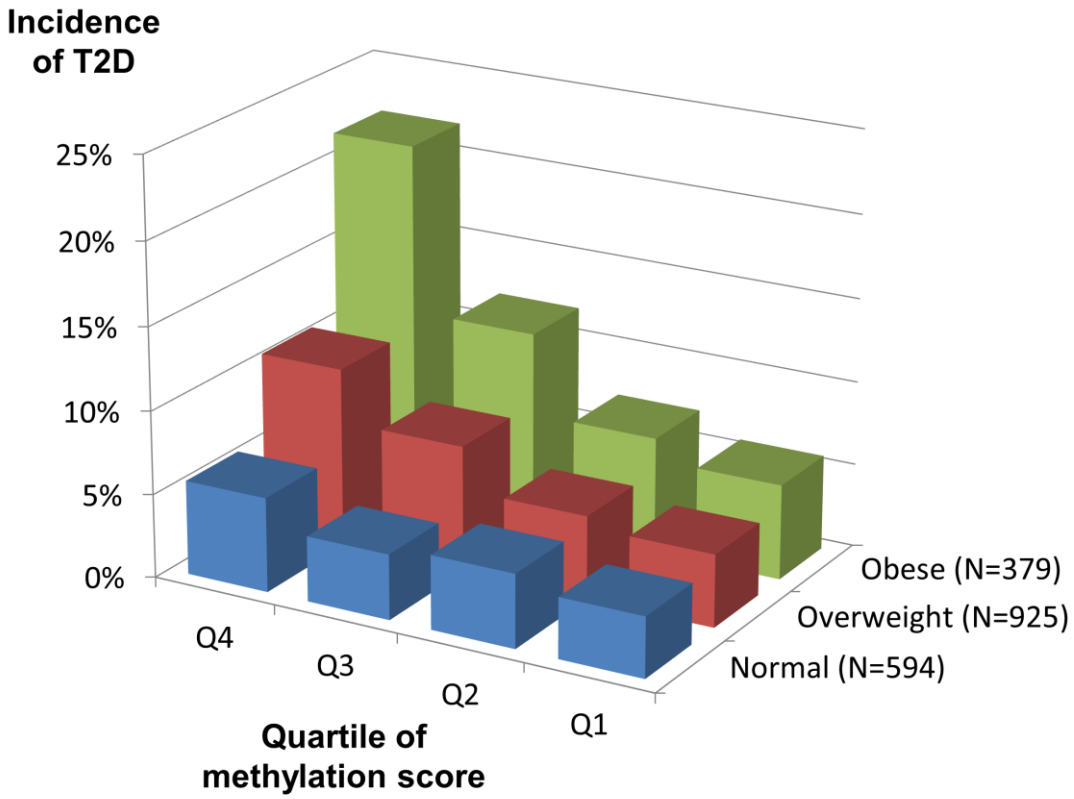


Figure 9. Targeted resequencing of the top locus by next generation sequencing. Bars present mean methylation at the CpG sites evaluated; the sentinel marker identified by EWAS is shown as a purple bar. The correlation track provides the correlation between methylation at each CpG site with the sentinel marker.

Inset: Relative risk for T2D for the methylation markers at the top locus identified by targeted resequencing. Results shown for: i. the 8 individual CpG sites assayed by pyrosequencing (green; light green for sentinel marker); ii. Sentinel marker by microarray (blue); and iii. Regional methylation scores (red). Results are as relative risk for T2D associated with 1SD reduction in methylation or methylation score. Score: sum of all 8 methylation markers.

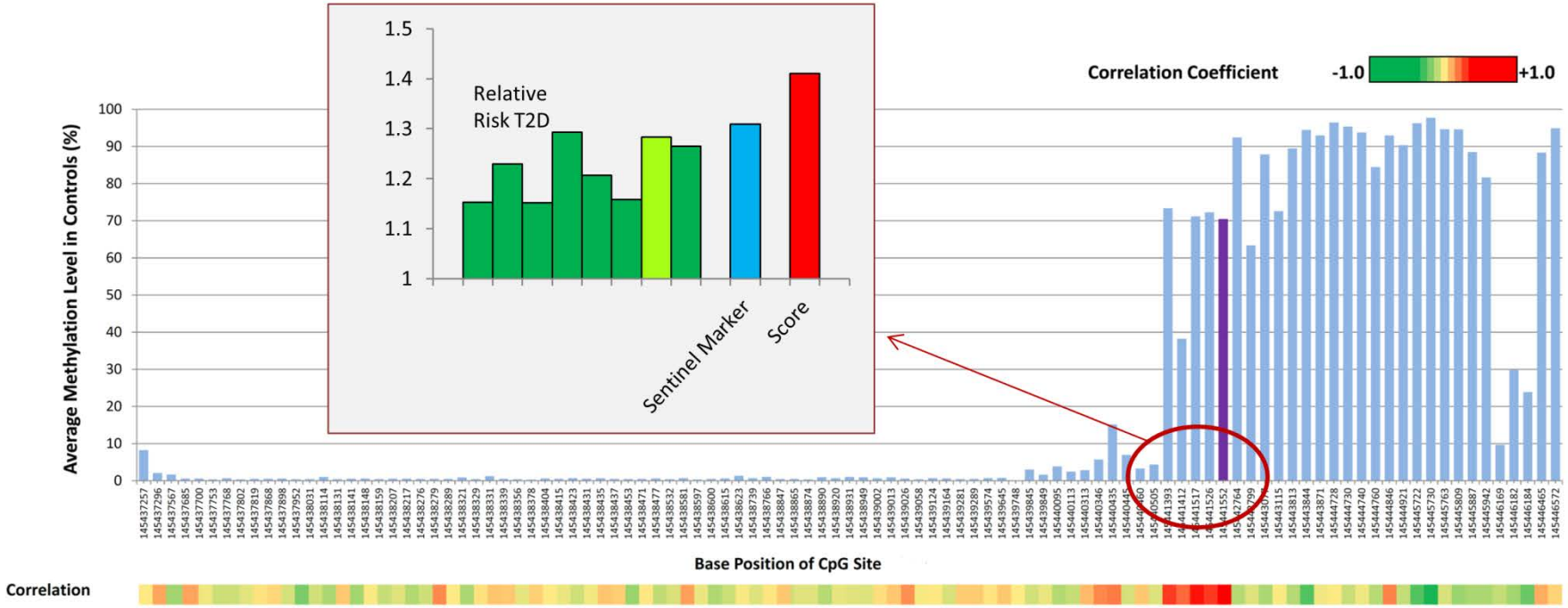
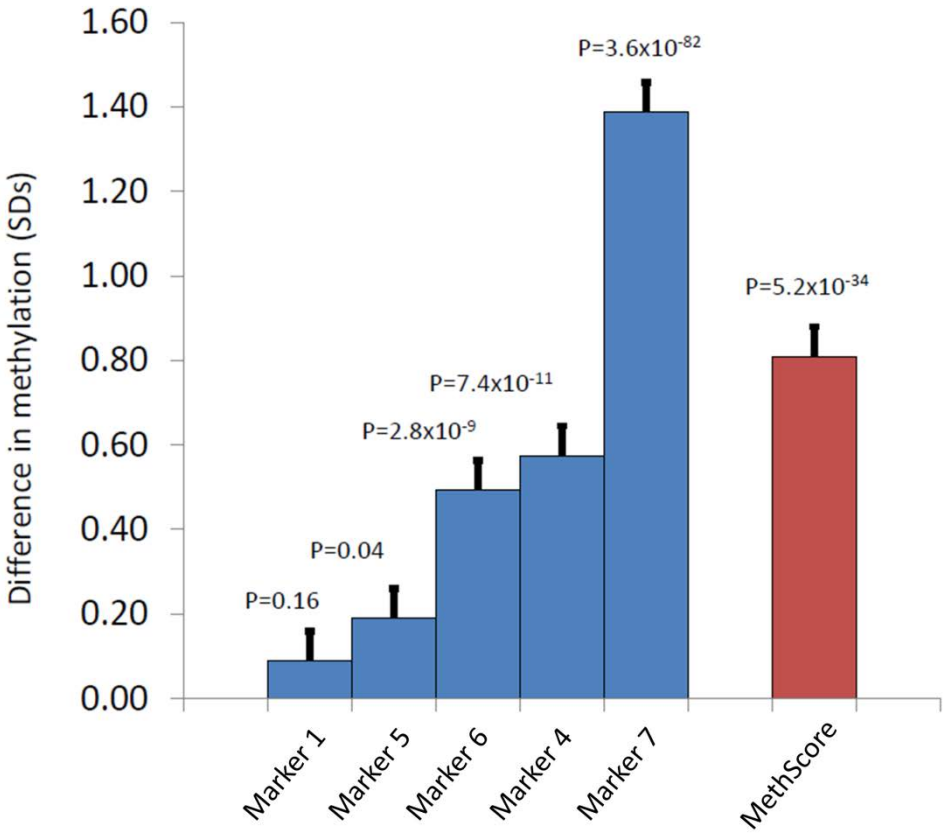


Figure 10. Difference in methylation between South Asians and Europeans without T2D. Results presented as the SD increase in methylation amongst South Asians compared to Europeans, aligned to the direction of effect for increased T2D risk, adjusted for age and gender.



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