Supplementary Methods

Genome-wide DNA methylation study

DNAs were bisulfite treated using the EpiTect® 96 Bisulfite Kit (Qiagen). 200 ng of bisulfite treated DNA of each sample was analysed using the Infinium Human Methylation 450K BeadChips (Illumina, San Diego, CA) according to the manufacture's protocol. The 450K BeadChips analyses 480,000 methylation sites covering 99% of RefSeq genes with an average of 17 CpG sites per gene across the promoter region, 5'-untranslated region (5'UTR), first exon, gene body and 3'-UTR and 96% of CpG islands.[1]

Validation of differentially methylated CpG sites by pyrosequencing

To validate the results of the array, quantitative DNA methylation analysis was performed by pyrosequencing [2] using the amplification and pyrosequencing primers detailed below. PCR was performed at 96 °C for 10 min, followed by 50 cycles at 95 °C for 10 sec, 10 sec at the respective annealing temperature and 72 °C for 10 sec. Methylation data were analyzed using the Pyro-Q-CpG software (Qiagen). The DNA methylation levels of *ALU* and *LINE1* elements were used as a surrogate marker for global DNA methylation levels and analyzed as previously reported.[3]

Gene	PCR primer forward	PCR primer reverse	PCR annealing temp(°C)	Pyrosequencing primer(s)
IFITM1	TTAGTTTAGGGATAGGAAGATGGTT	Biotin-AAAACAAAACCAAAAAAACAAAAAC	56	TAGATAATATAGGAAAAA
IFITM3	GGGTAGTGTAGGGGTTGATTAATTT	Biotin-TCAAAAAACATCACTAAAACCAAAA	58	TTGAATGTTATTGTAGAAAA
IFI44L AMP 1	TTATGTTAGTGTGGATTGAGTGAAG	Biotin-TCCTACATTTATTAATTAAAATTTAAAATT	56	AATGTTTTATGAATTTAGT GGGATAGTTATAGTGTTTAT
IFI44L AMP 2	ATAAGGAATTGAATTTTGTTAATAATTATA	Biotin-TATAAAAAACCTTAAAACATCTACC	58	TGTTGTTTTAAGTTTTTA
IRF5	TTTTTTAGGGTTGTTTATTGGATGT	Biotin-TCAAAACCCATAACTTTAAAAATTC	54	TATATATTTTATTTAGAGAT
RUNX3 AMP1	TAGTTTGGGGTTAATAATTTTTTTT	Biotin-ACCACTACTATTTTTCTTTTACCACC	56	GAGGTTTGTAAAATG
RUNX3 AMP2	TTTATTTGTGAGGTTGGTTTTAGTA	Biotin-AAATAACATAACAAAAAACTCTCC	56	GGTTTAAGAAATAGAATTGA
TNFAIP8 AMP1	TGTTTTTTTTAAGGTTGGTTTATTG	Biotin-AAAACATCCAAAAACAATTTTCTTAC	56	TGGTTAGTTATTATTATTTA
TNFAIP8 AMP2	TTTGATTTAGGATGTGTGGTAGAG	Biotin-AAAAAATATAACCAACCAAAAAAAA	56	GAAGGGTGTAGTTTGT
IKZF1 AMP1	AAAAGGATAGAAAGTAATGTGGATTTAAA	Biotin-AACATTATTTTATTTTTCAAAATAAACTAA	58	AATTTAAATAAATTTTAGTG
IKZF1 AMP2	Biotin-GGTTTTATTTAGTATTTGTTTTTTTATGT	ACTCTTAAAACTTTACTATCCTCCC	56	ATACCTAAACTTCCCCC
IKZF1 AMP3	TTGAATGTGAGTTTTTTTTAAATTGAG	Biotin-AAACACTTAAATCCTATCACACTCCTT	56	ATTGAGGTTATATTAAGTTT
SLC15A4	GTTTGAGGTTTTGATTTTTGTAGGA	Biotin-ATATACACTTTATTTTCCCATTTTACCC	56	AATGAATAGGTTTTATTAGA
GRB2	AAAGTGAGAGGGTTATAGGGTGATT	Biotin-CTCAAACCCCAACTAATAAAAAAAA	56	TTTTTGATTTTTAGA
MIR21	TTTATATGTTAATTTAGTTTTTTTGT	Biotin-CAAACATTTCTAACCTATTAAAATC	51	ATAGAATAGAATTGGGGTT
IL21R	GGTGTAGAGTTTGATGGGATTTATTT	Biotin-TCTCCTCCACATACACAAAAAACTA	64	GGTTGGTGTGTTTATT
CXCR5	GGGAGTTTATAGGTTAAGTTAGTATT	Biotin-CAACTTATATTTTTAAATCCTCATATAC	58	AATTGAAGTTTTGTGATTTT
TRAF5	TGAGGTAGGAGAATTGTTTGAATTT	Biotin-TAAACCTAATCATCCCCATTTTACA	64	TTAGTTGTAGAGTTTGTTGA

Statistical analyses

Raw signals of 450K BeadChips were extracted using the GenomeStudio® software (v2011.1, Illumina). The DNA methylation level of each CpG was calculated as the ratio of the intensity of fluorescent signals of the methylated alleles to the sum of methylated and unmethylated alleles (β value). A refined version of the SQN pipeline [4] including a revised annotation file [5] was used for data processing, correction and normalization. Intensity values were corrected for potential biases in fluorescent dye intensity and background corrected using the *lumi* R package [6] as implemented in the SQN pipeline. Probes potentially influenced by SNPs underlying the entire sequence of the probe (+1 or + 2 bases depending on the Infinium probe type) that are present in the EUR population of the 1000 Genome project (http://www.1000genomes.org) at a frequency of more than 5 % were removed from the analysis. Furthermore, probes previously reported to map to several genomic regions were removed.[7] The Subset Quantile Normalization pipeline uses then the intensity signals of high-quality (i.e. low detection p-value) Infinium I probes as "anchors" to estimate a reference distribution of quantiles for probes in a biologically similar context based on the annotation file.[4] This reference is then used to estimate a target distribution of quantiles for InfII probes as a means to provide an accurate normalization of InfI/InfII probes and correct for the shift. SQN is performed for each individual separately. As principal component analysis as well as hierarchical clustering did not show an overall difference in the methylation patterns between patients and controls, a quantile normalization was performed for between sample normalization.

References

1 Sandoval J, Heyn H, Moran S, *et al*. Validation of a DNA methylation microarray for 450,000 CpG sites in the human genome. *Epigenetics* 2011;**6**(6):692-702.

2 Tost J, Gut IG. Analysis of gene-specific DNA methylation patterns by pyrosequencing technology. *Methods Mol Biol* 2007;**373**:89-102.

3 Yang AS, Estecio MR, Doshi K, Kondo Y, Tajara EH, Issa JP. A simple method for estimating global DNA methylation using bisulfite PCR of repetitive DNA elements. *Nucleic Acids Res* 2004;**32**(3):e38.
4 Touleimat N, Tost J. Complete pipeline for Infinium((R)) Human Methylation 450K BeadChip data processing using subset quantile normalization for accurate DNA methylation estimation. *Epigenomics* 2012;**4**(3):325-41.
5 Price ME, Cotton AM, Lam LL, *et al*. Additional annotation enhances potential for biologically-relevant analysis of the Illumina Infinium HumanMethylation450 BeadChip array. *Epigenetics chromatin* 2013;**6**(1):4.
6 Du P, Kibbe WA, Lin SM. lumi: a pipeline for processing Illumina microarray. *Bioinformatics* 2008;**24**(13):1547-8
7 Chen YA, Lemire M, Choufani S, *et al*. Discovery of cross-reactive probes and polymorphic CpGs in the Illumina Infinium HumanMethylation450 microarray. *Epigenetics* 2013;**8**(2):203-9.