IEEE BIBM 2010 Tutorial

Epigenomics and cancer

DNA methylation and cancer

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LETTERS

Genome-scale DNA methylation maps of pluripotent and differentiated cells

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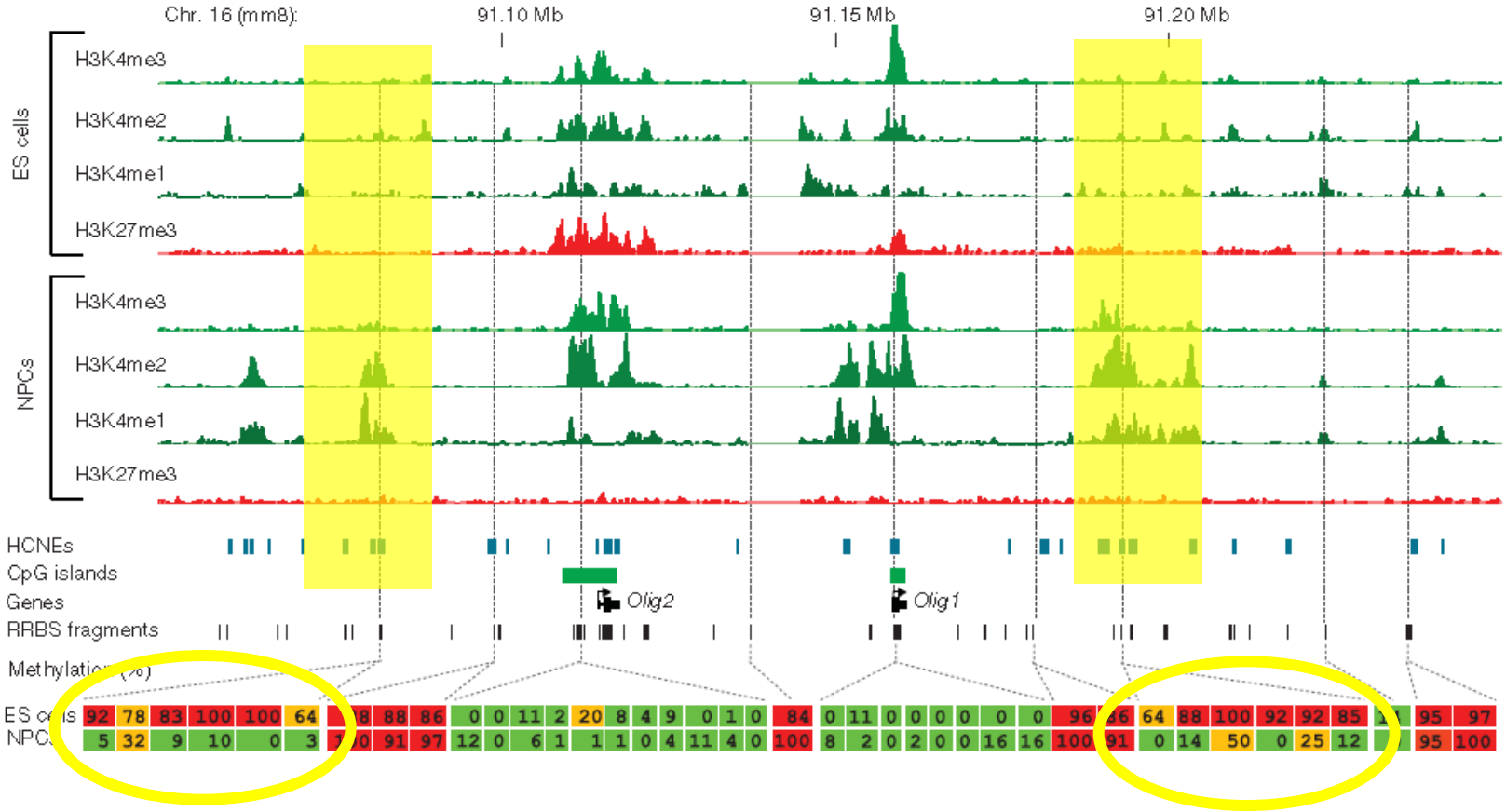
Aim: To study how DNA methylation changes during cellular differentiation and how it relates to chromatin modifications

Methods: Genome-wide DNA methylation profiles at nucleotide resolution by reduced representation bisulphite sequencing (RRBS)

Samples: Mouse ESCs, ESC-derived neural cells and other primary tissues

Drawback: Complexity reduction approach based on certain restriction enzyme (only 4.8% of all CpGs but includes sequences from 90% of all CpG islands)

Developmentally regulated de-methylation of highly conserved non-coding elements (HCNEs)



Key findings: Methylation of CpGs are dynamic epigenetic marks that undergo extensive changes during cellular differentiation, particular in regulatory regions outside of core promoters

nature genetics

The human colon cancer methylome shows similar hypo- and hypermethylation at conserved tissue-specific CpG island shores

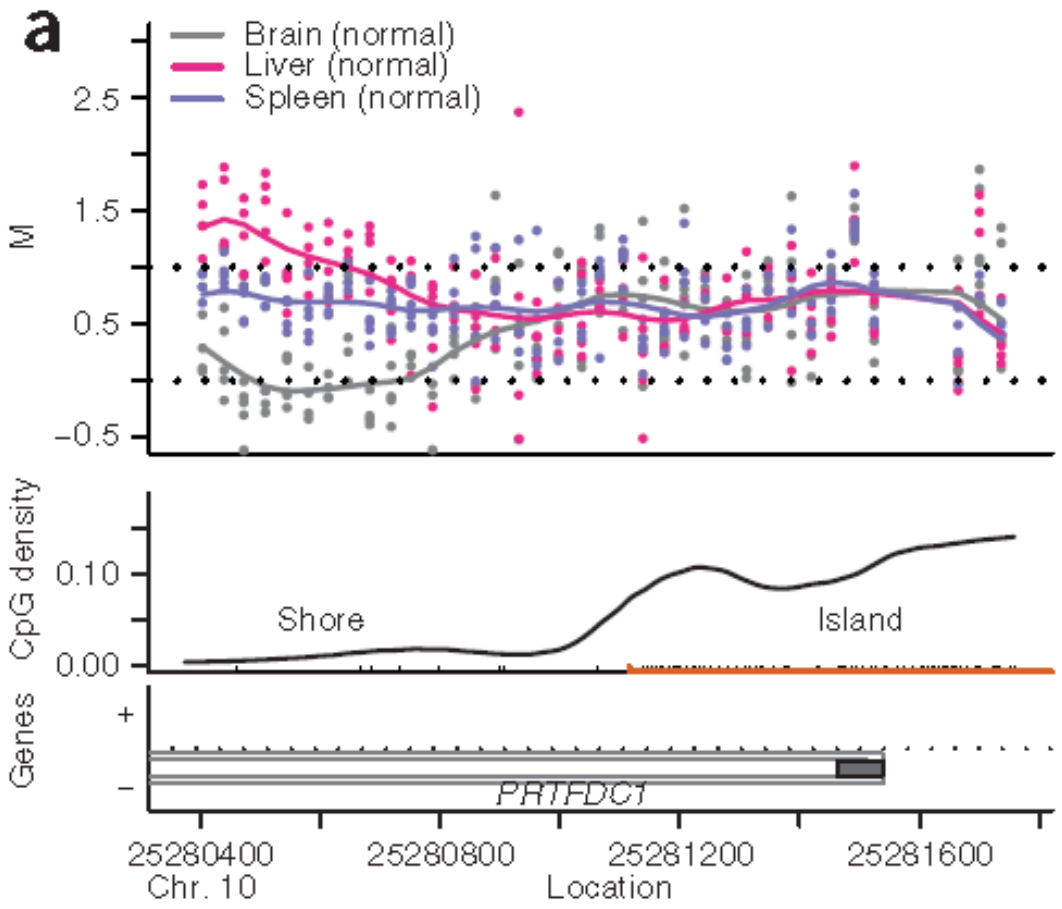
Rafael A Irizarry[1,2,8], Christine Ladd-Acosta[2,3,8], Bo Wen[2,3], Zhijin Wu[4], Carolina Montano[2,3], Patrick Onyango[2,3], Hengmi Cui[2,3], Kevin Gabo[2,3], Michael Rongione[2,3], Maree Webster[5], Hong Ji[2,3], James B Potash[2,6], Sarven Sabunciyan[2,7] & Andrew P Feinberg[2,3,8]

Aims: To localize the sites of DNA methylation that distinguish 1) cancer from normal tissues and 2) different tissues

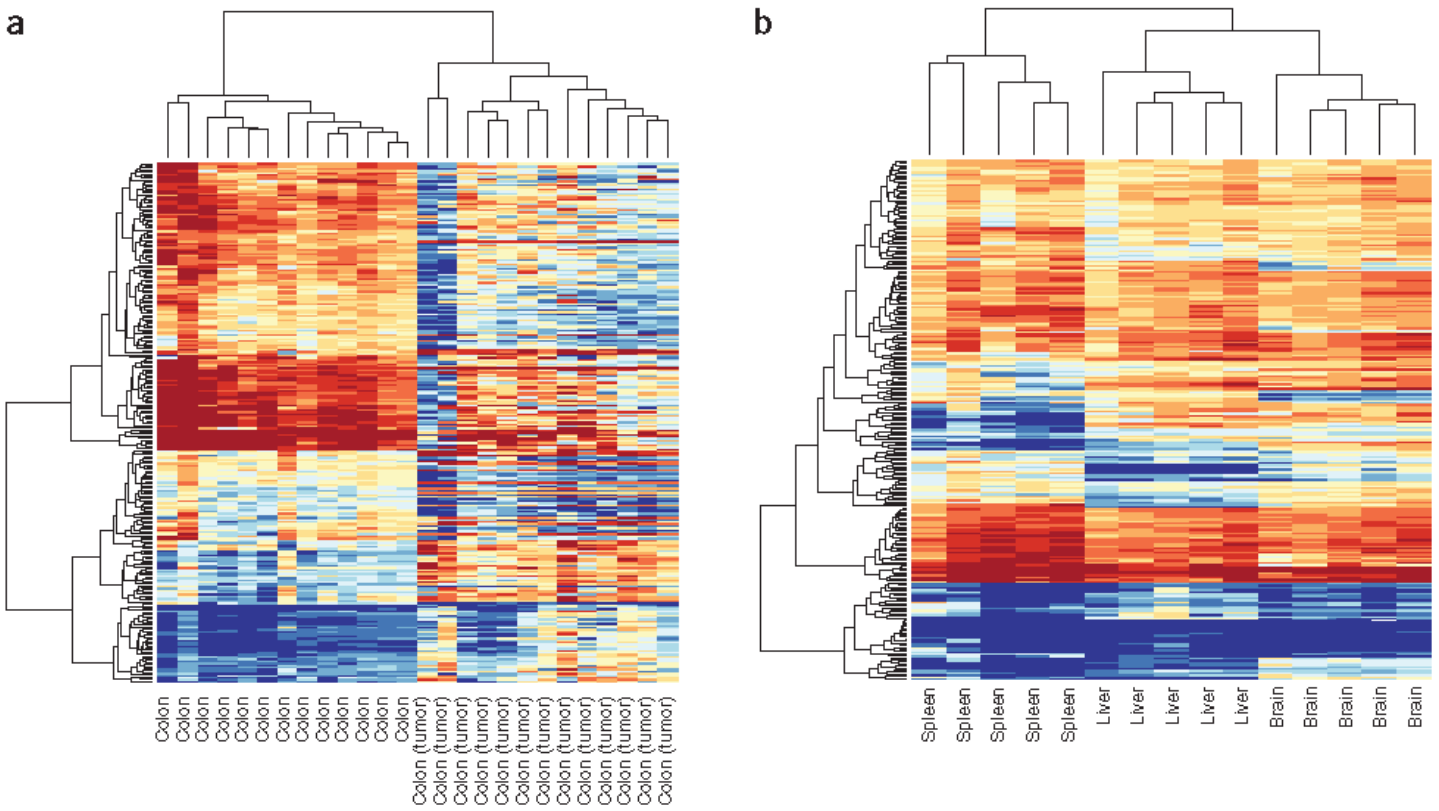
Methods: Investigation of CpGs throughout the genome (both high- and low-CpG density regions) by comprehensive high-throughput array-based relative methylation (CHARM)

Samples: 13 colorectal cancers and matched normal mucosa, normal tissue types from endodermal (liver), mesodermal (spleen) and ectodermal (brain) lineages

Most tissue-specific differential DNA methylation is located at CpG island shores (up to 2-kilobase)



Overlap between cancer-related and tissue-specific CpG island shore methylation



Key findings:

1) Most methylation changes of colon cancer occurs in 'CpG island shores', rather than promoters or CpG islands.

2) Methylation changes in cancer are at sites that vary normally in tissue differentiation i.e. Epigenetic alterations affecting tissue-specific differentiation are critical in cancer formation

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LETTERS

Comprehensive methylome map of lineage commitment from haematopoietic progenitors

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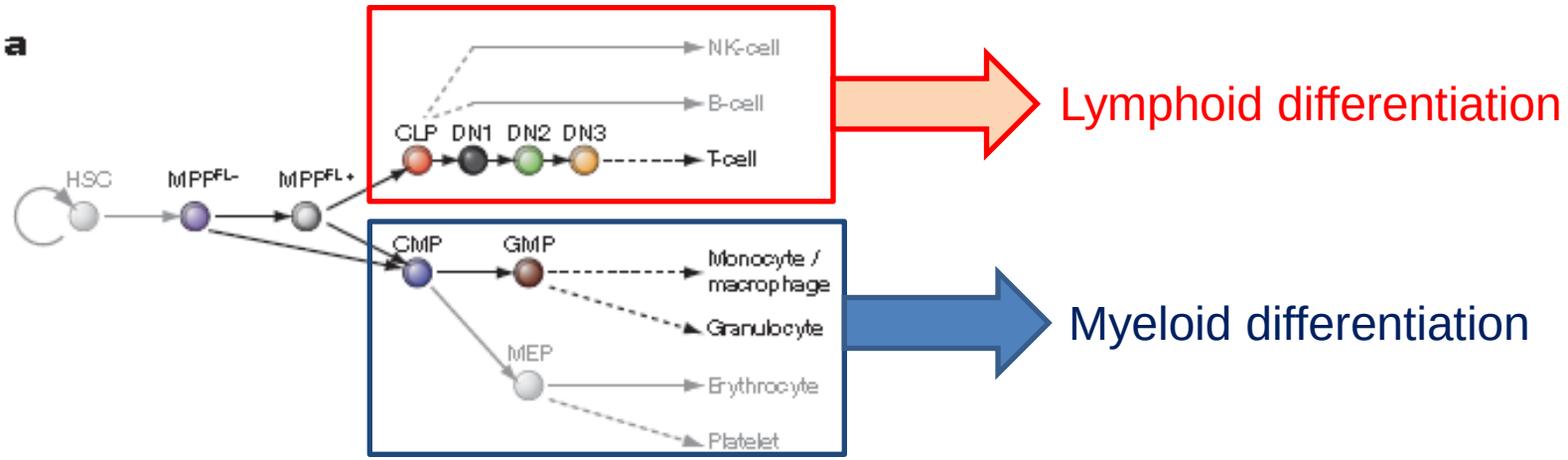
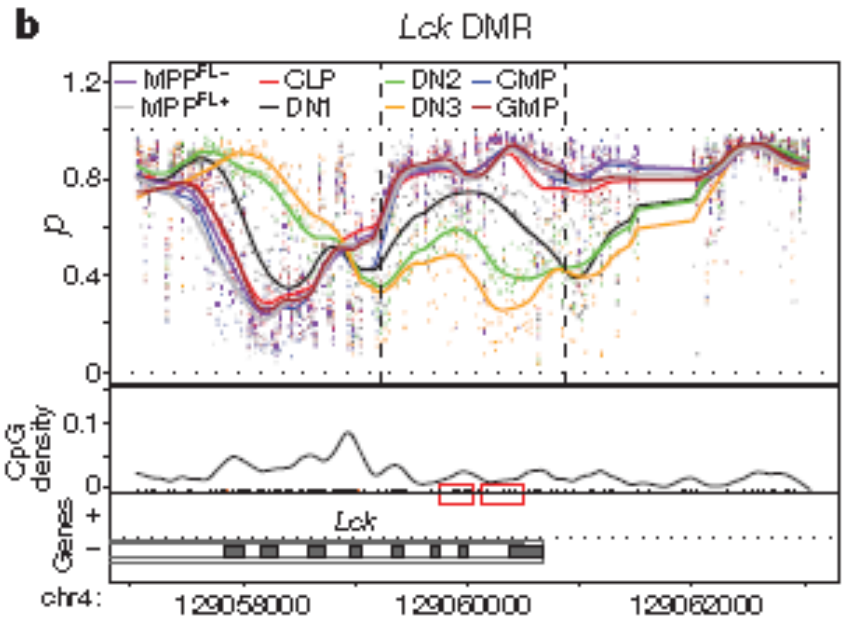
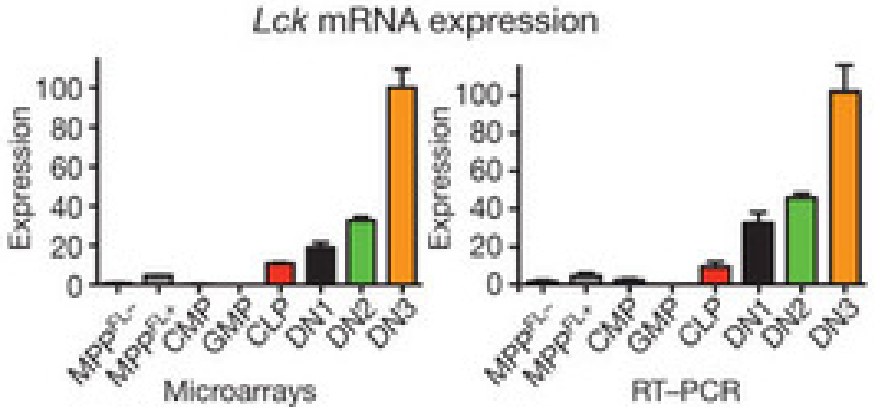
Aim: To investigate the change of methylome during cell-fate decisions (using the model of haematopoiesis)
Methods: 4.6 million CpG sites per genome examined by CHARM (array-based)
Samples: Mouse multipotent progenitors, myeloid and lymphoid progenitors (8 cell populations)

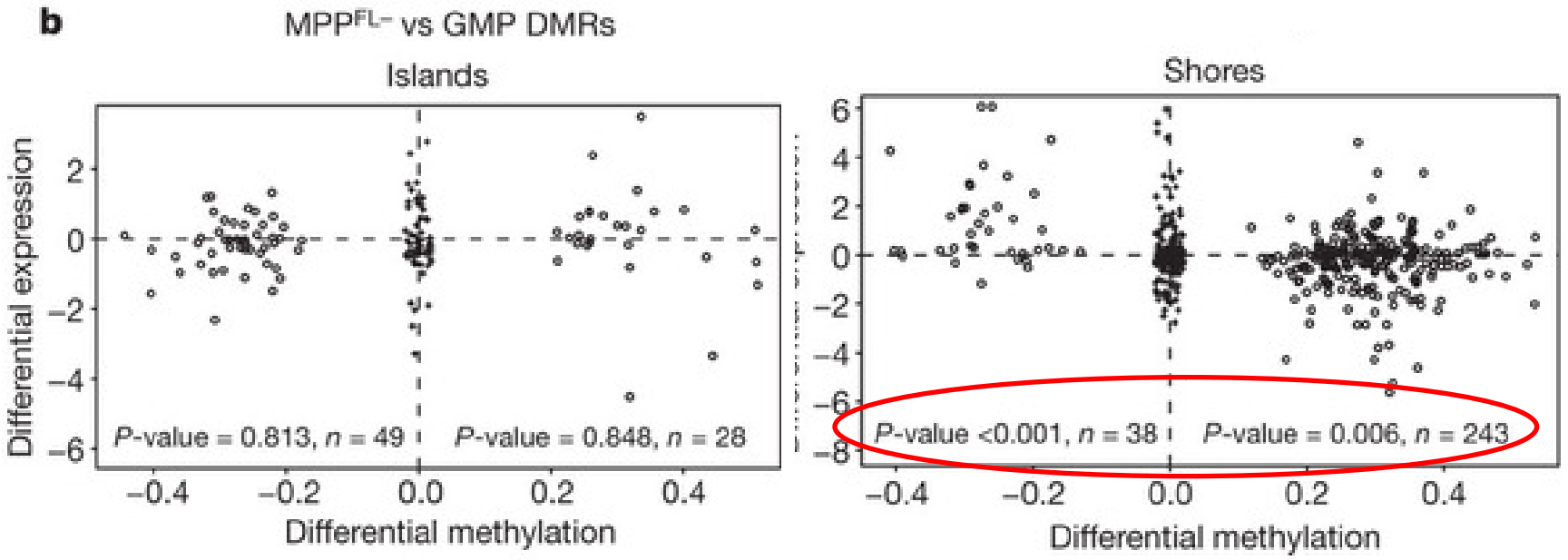


Differential DNA methylation between lymphoid and myeloid progenitors at CpG island shores





Differential DNA methylation correlates with gene expression more strongly at CpG island shores than CpG islands



Key findings: Marked epigenetic plasticity accompanied both lymphoid and myeloid restriction → Modulation of DNA methylation occurs during lineage-specific differentiation.

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ARTICLES

Human DNA methylomes at base resolution show widespread epigenomic differences

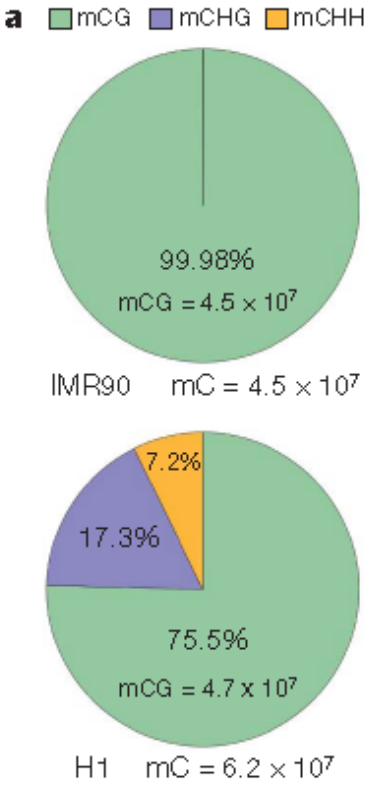
Ryan Lister[1]*, Mattia Pelizzola[1]*, Robert H. Dowen[1], R. David Hawkins[2], Gary Hon[2], Julian Tonti-Filippini[4], Joseph R. Nery[1], Leonard Lee[2], Zhen Ye[2], Que-Minh Ngo[2], Lee Edsall[2], Jessica Antosiewicz-Bourget[5,6], Ron Stewart[5,6], Victor Ruotti[5,6], A. Harvey Millar[4], James A. Thomson[5,6,7,8], Bing Ren[2,3] & Joseph R. Ecker[1]

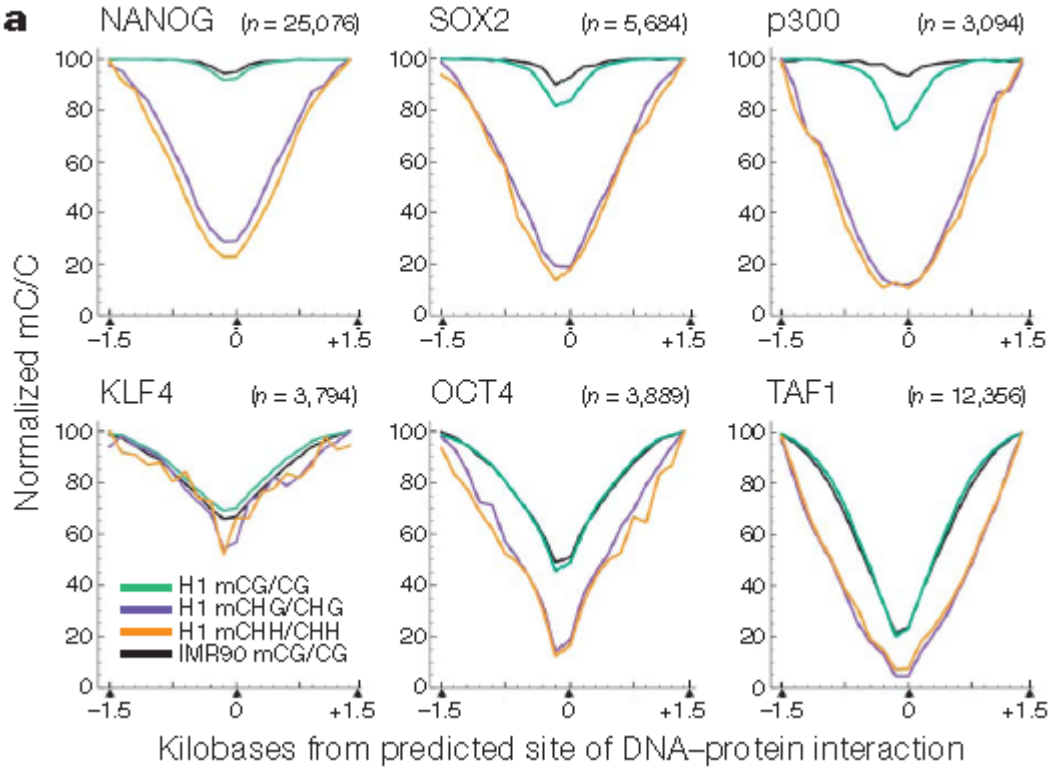
Aims: To understand how changes in DNA methylation patterns and histone modifications affect readout of proximal genetic information

Methods: First genome-wide (94% of cytosines in human genome), single-base-resolution DNA methylation mapping by bisulfite genome sequencing (MethylC-Seq), accompanied with ChIP-seq and transcriptome profiling

Samples: Human ESC cell line (H1) and fetal lung fibroblast cell line (IMR90)

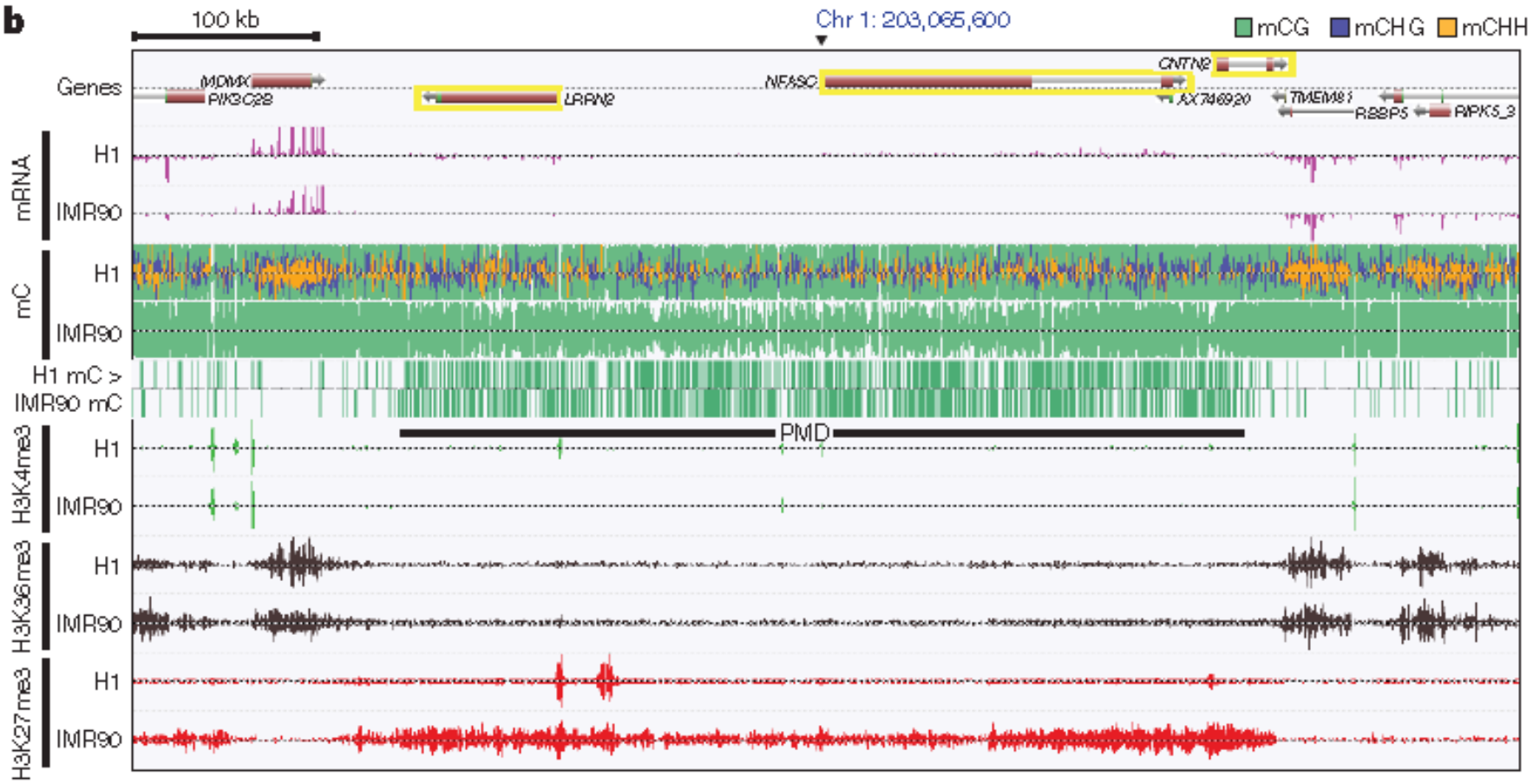
ESC-specific methylation in non-CG context





- ~25% of all methylation in ESC was in a non-CG context
- Enrichment in gene bodies and depletion in protein binding sites and enhancers
- Non-CG methylation disappeared upon induced ESC differentiation, and was restored in iPS cells

Widespread cell-specific patterns of DNA methylation



Key findings: Different patterning of CG and non-CG methylation suggests that ESCs use a yet-to-be identified methylation mechanism to affect gene regulation.

Take-home message: Non-CpG island sites matter!

- Unbiased genome-wide high-resolution methylation analyses reveal previously unidentified sites of methylation i.e. CpG island shores, non-CG context
- Methylation of genes involved in tissue-specific differentiation are prominent mechanism of cancer development