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# The Evolving Role of MeCP2 in Human Neurodevelopmental Disorders

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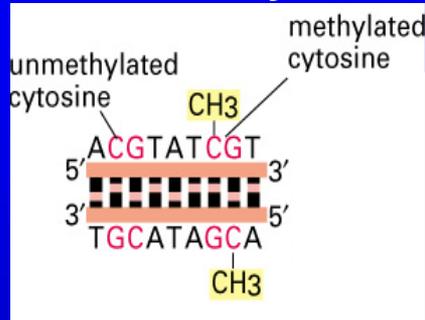
UC Davis M.I.N.D. Institute



# What is Epigenetics?

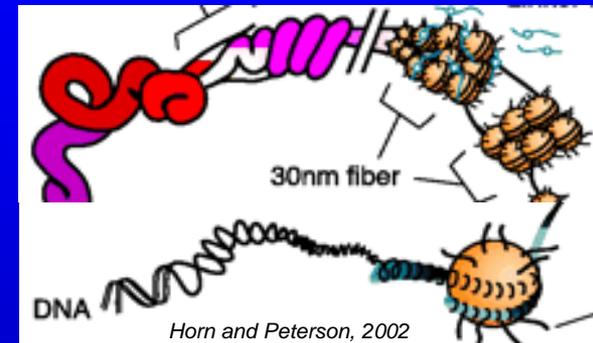
Multiple layers of epigenetic codes

## DNA methylation

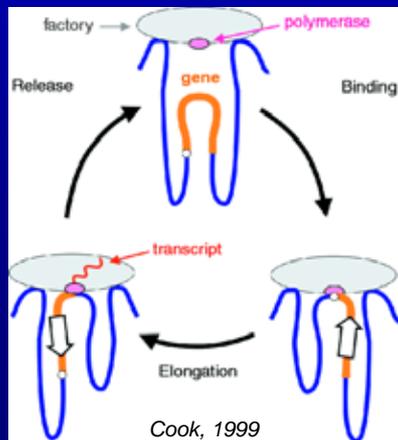


**Inherited and reversible modifications to nucleotides or chromosomes that do not change the sequence but can alter gene expression**

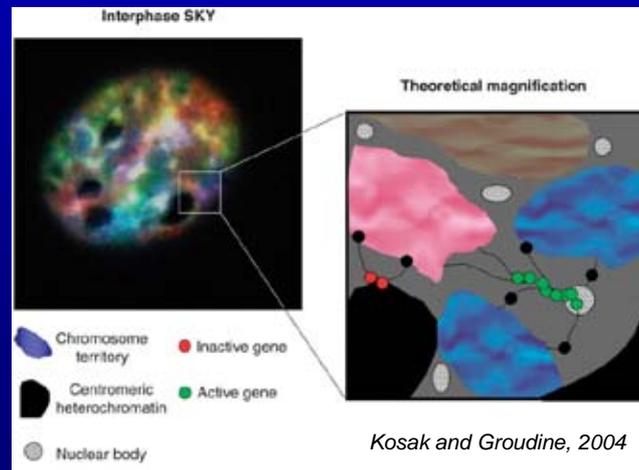
## Histone modifications



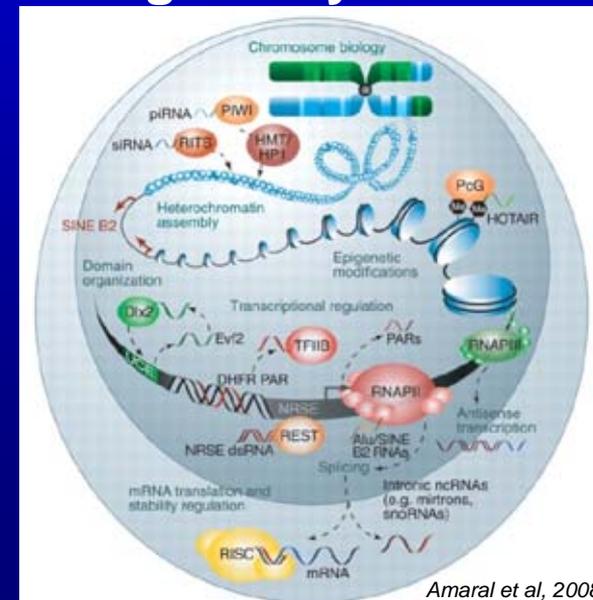
## Chromatin structure



## Spatial organization of chromosomes



## Regulatory RNAs



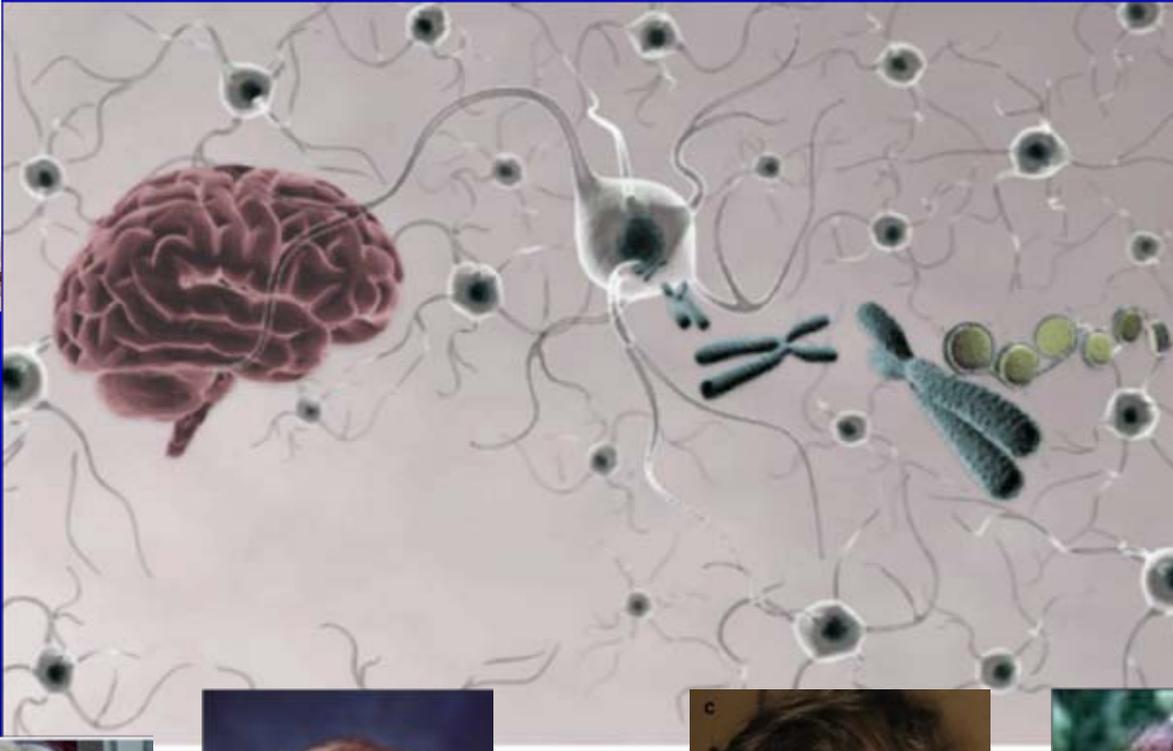
# The Epigenetic Interface in Autism-Spectrum Disorders



RETT



IDIC15



FRAGILE X



DOWN



PRADER-WILLI



ANGELMAN



RUBINSTEIN-TAYBI



WILLIAMS

# MECP2 in Rett syndrome and beyond

QuickTime™ and a decompressor are needed to see this picture.

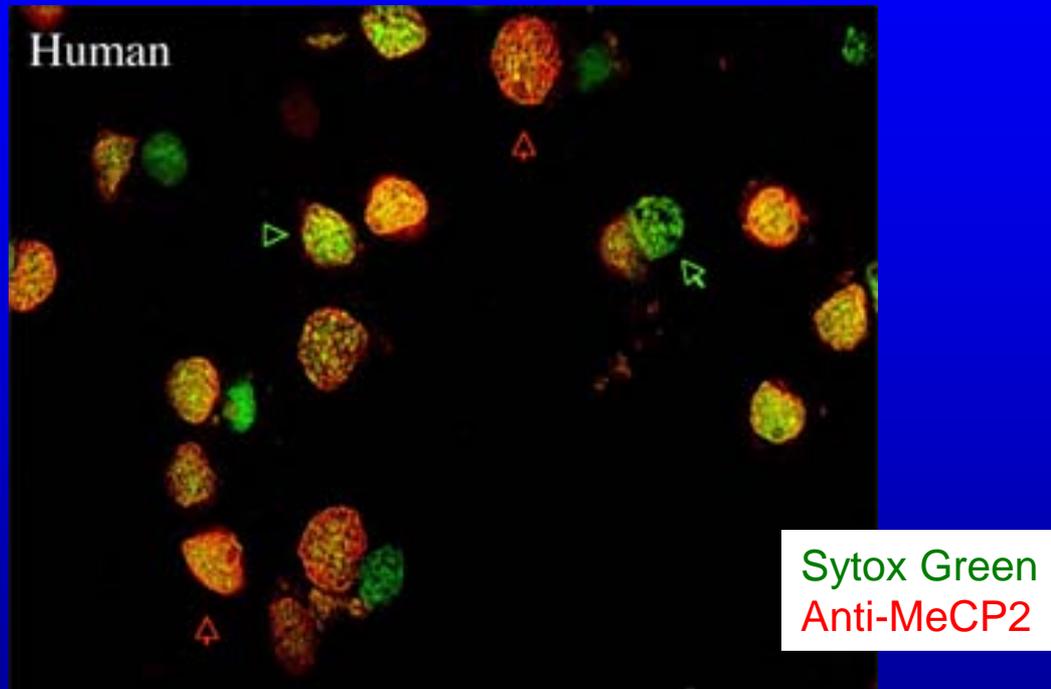


*Gonzales and LaSalle, 2010*

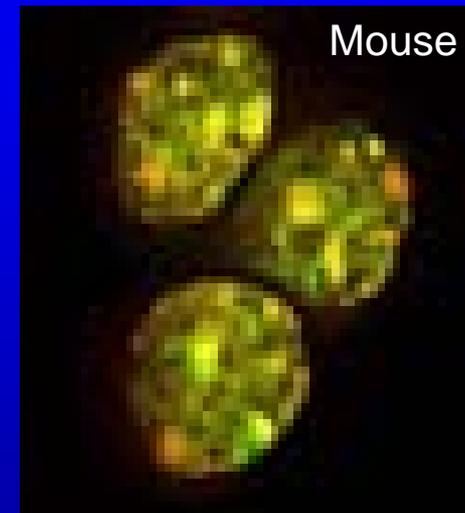
- Rett syndrome (RTT)
- X-linked dominant, females are heterozygous for MECP2 mutations
- ~1/10,000 in US population
- Neurodevelopmental regression around 6 to 18 months of age
- MECP2 encodes a known epigenetic factor, methyl CpG binding protein 2
- MECP2/MeCP2 is epigenetic at two levels: X chromosome inactivation and “reader” of DNA methylation marks

# A “bird’s eye view” of MeCP2

MeCP2 is a marker for mature neurons in the post-natal mammalian brain

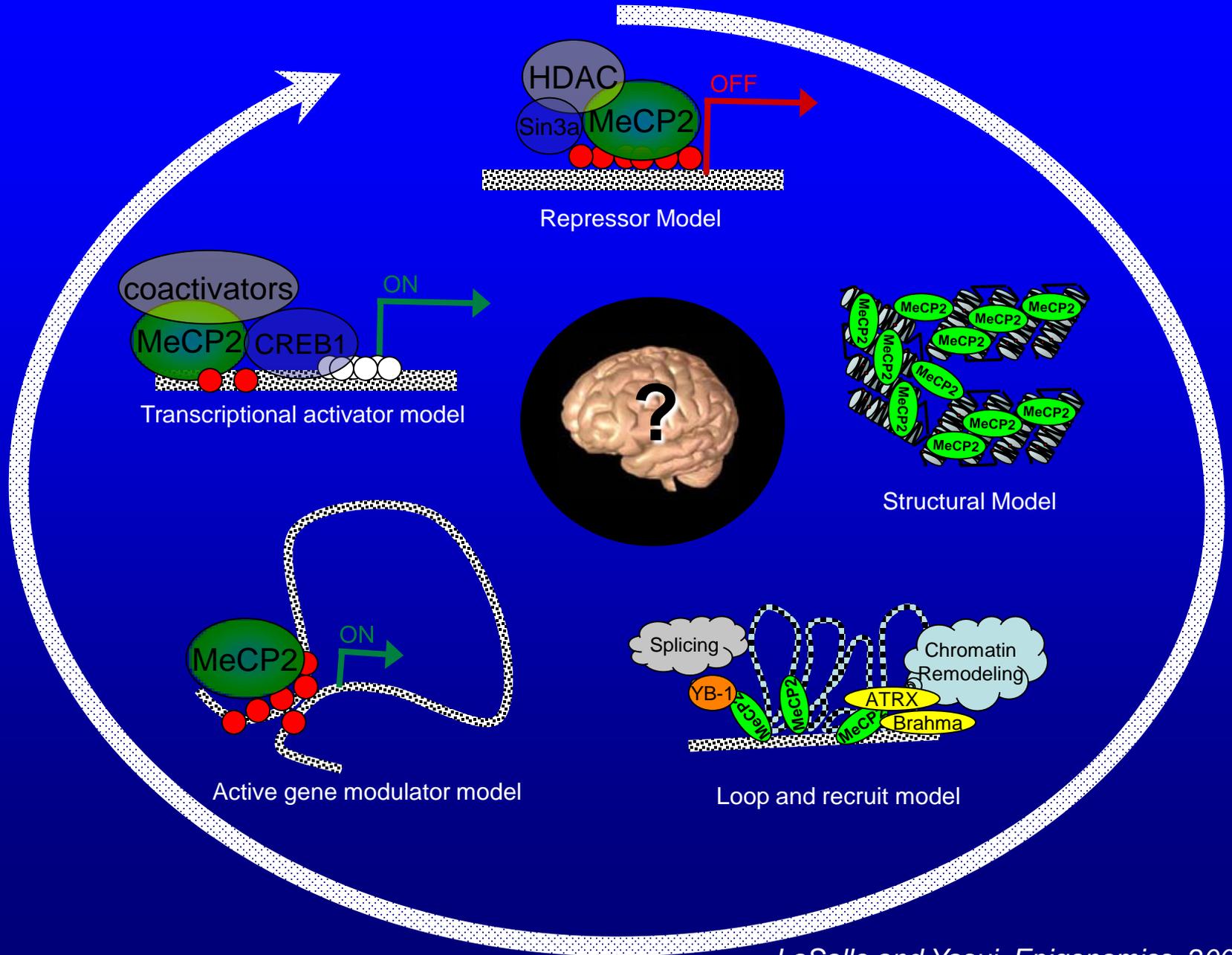


MeCP2 localizes to both inert nuclear heterochromatin as well as non-heterochromatic regions



- Highlights from Skene *et al*, *Mol. Cell* 2010 ChiP-seq analysis of MeCP2 binding
- Neuronal nuclei have about one molecule of MeCP2 for every two nucleosomes
  - MeCP2 in neurons binds chromosome-wide, tracking the density of DNA methylation
  - MeCP2 deficiency doubles both histone acetylation and histone H1 only in neurons

# Evolving models of MeCP2 come full circle



# What type of genes does MeCP2 regulate?

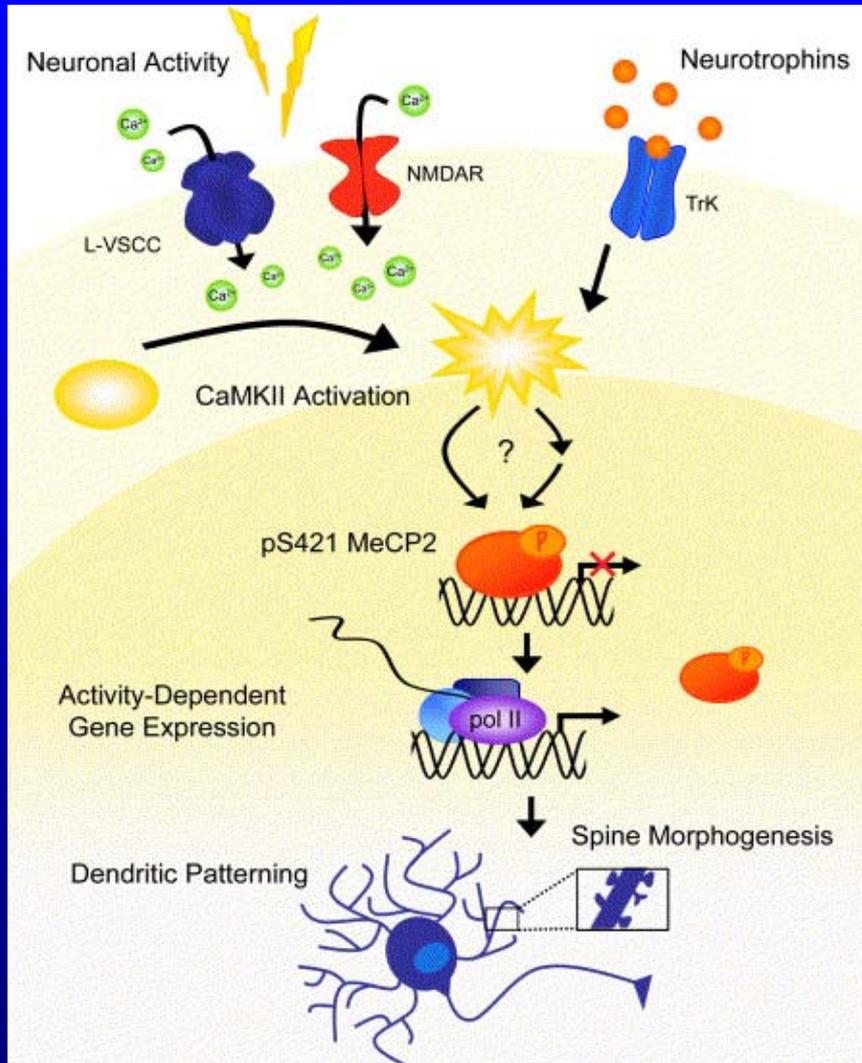
MeCP2 regulates the regulators!

Especially activity-dependent regulators

From Singh, Saxena, Christodoulou, and Ravine, *NAR*, 2008

Gene	Function	References
<i>xHairy2a</i>	Neuronal repressor	(56)
<i>BDNF/Bdnf</i>	Long term potentiation	(81,90)
<i>IGF2</i>	Cell proliferation	(91)
<i>MPP1</i>	Signal transduction	(91)
<i>UBE3A/Ube3a</i>	Proteolysis	(92,93)
<i>GABRB3/Gabrb3</i>	GABA receptor subunit	(92)
<i>DLX5/Dlx5</i>	Transcription factor	(40)
<i>Dlx6</i>	Transcription factor	(23,40)
<i>Fkbp5</i>	Hormone signalling	(94)
<i>Sgk1</i>	Ion channel activation	(94)
<i>ID1/Id1, ID2/Id2, ID3/Id3</i>	Transcriptional regulation	(95)
<i>Uqcrc1</i>	Mitochondrial respiratory complex subunit	(59)
<i>Crh</i>	Anxiety and stress response	(96)
<i>IGFBP3/Igfbp3</i>	Hormone signalling	(97)
<i>FXYD1/Fxyd1</i>	Na <sup>+</sup> /K <sup>+</sup> -ATPase activity	(98,99)
<i>Reln</i>	Cell signalling	(99)
<i>Gtl2/Meg3</i>	Non-coding RNA	(99)
<i>JUNB</i>	Early response gene, Oncogene	(42)
<i>RNASEH2A</i>	Ribonucleotide cleavage from RNA-DNA complex	(42)
<i>Sst</i>	Hormone signalling	(43)
<i>Oprk1</i>	Opioid receptor	(43)
<i>Gamt</i>	Methyltransferase	(43)
<i>Gprin1</i>	Neurite formation	(43)
<i>Mef2c</i>	Myogenesis	(43)
<i>A2bp1</i>	Splicing	(43)
<i>Creb1</i>	Transcriptional co-activator	(43)

# MeCP2 is modified in response to environmental stimuli and neuronal activity



Post-translational modifications of MeCP2 may be instrumental to understanding its diverse functions

phosphorylation

- pS421
- pS80
- pS229

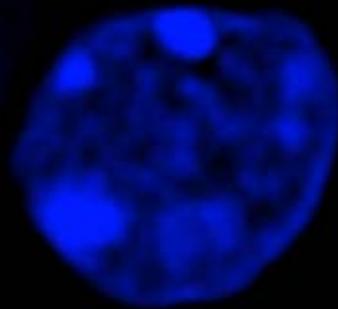
acetylation and ubiquitylation

# What is the essential role for MeCP2 in neuronal maturation?

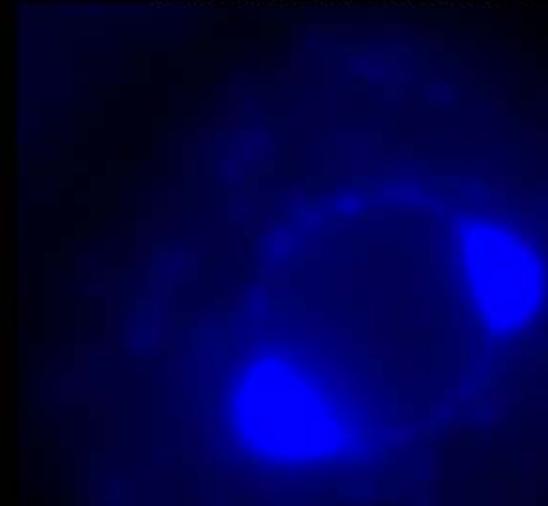
**Act locally, think globally!**

Maturation of neurons is characterized by distinctive changes to nuclear size, nucleolar size, and chromatin distribution

Embryonic neuronal nucleus



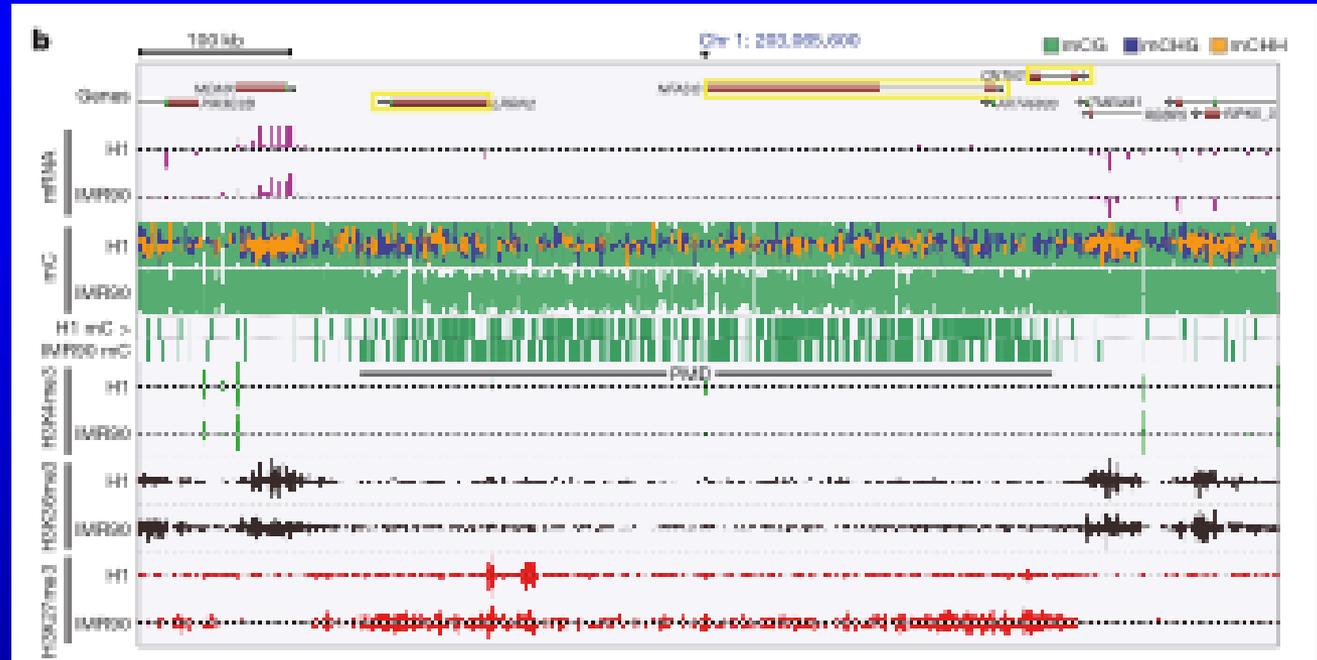
Mature adult neuronal nucleus



DNA dye (DAPI) of mouse cortical neurons

# Analysis of neuronal methylome “landscape” partially methylated domains (PMD) vs highly methylated domains (HMD)

MethylC-seq  
Base pair  
resolution of %  
methylation  
genome-wide



PMDs from *Lister et al, Nature, 2009*

- Large domains of partial methylation (<70%)
- Observed in IMR-90 fetal lung fibroblast, but not in H1 embryonic stem cell
- Contained genes with lower expression values than genes in fully methylated regions in IMR-90
- Co-occur with H3K27me3 or H3K9me3 repressive marks

Partially methylated domains are observed in human neuronal cell line SH-SY5Y

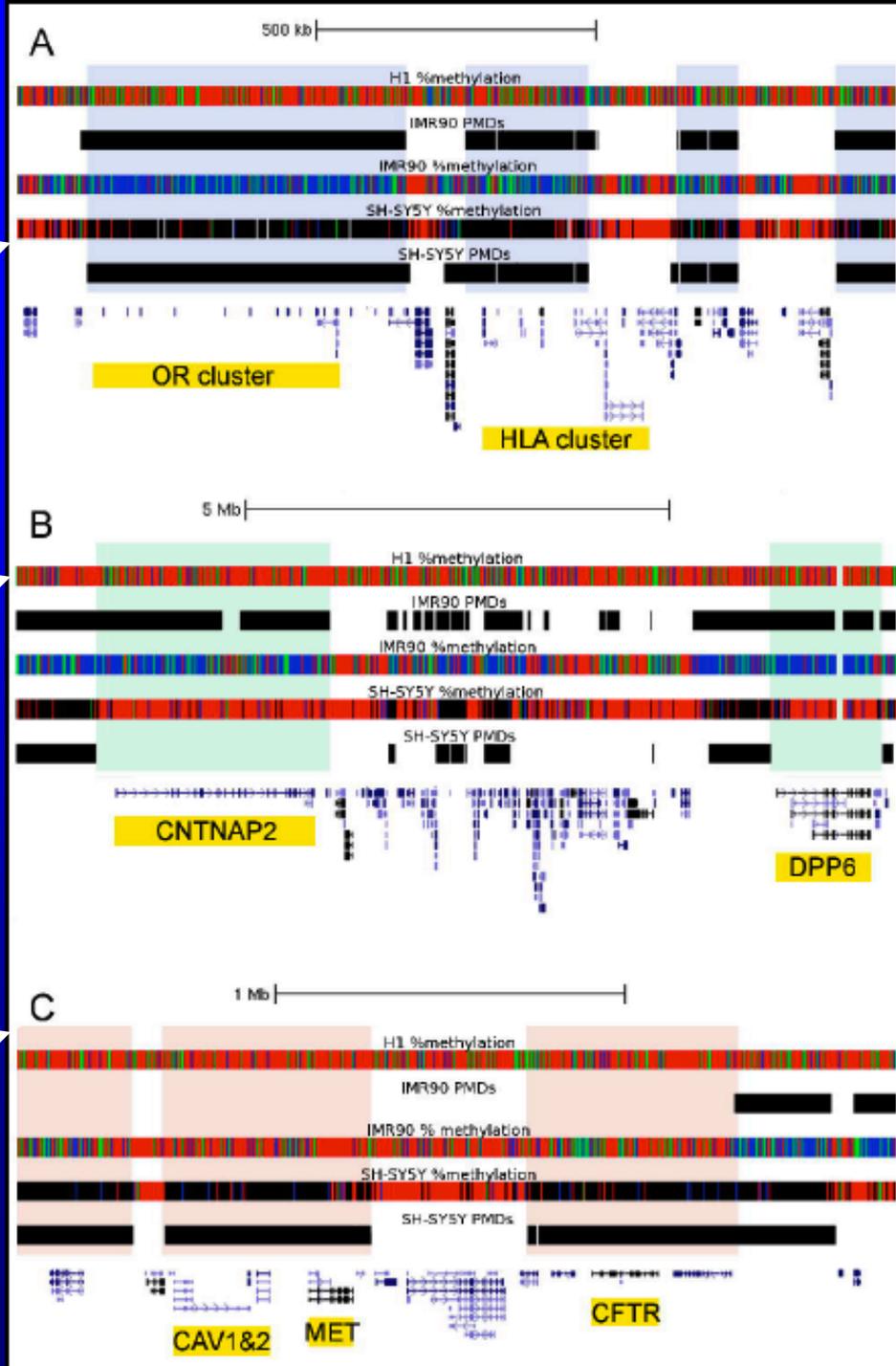
PMD in both neuron and lung (B-PMD)

PMD in lung but highly methylated in neuron (N-HMD)

PMD in neuron but highly methylated in lung (L-HMD)

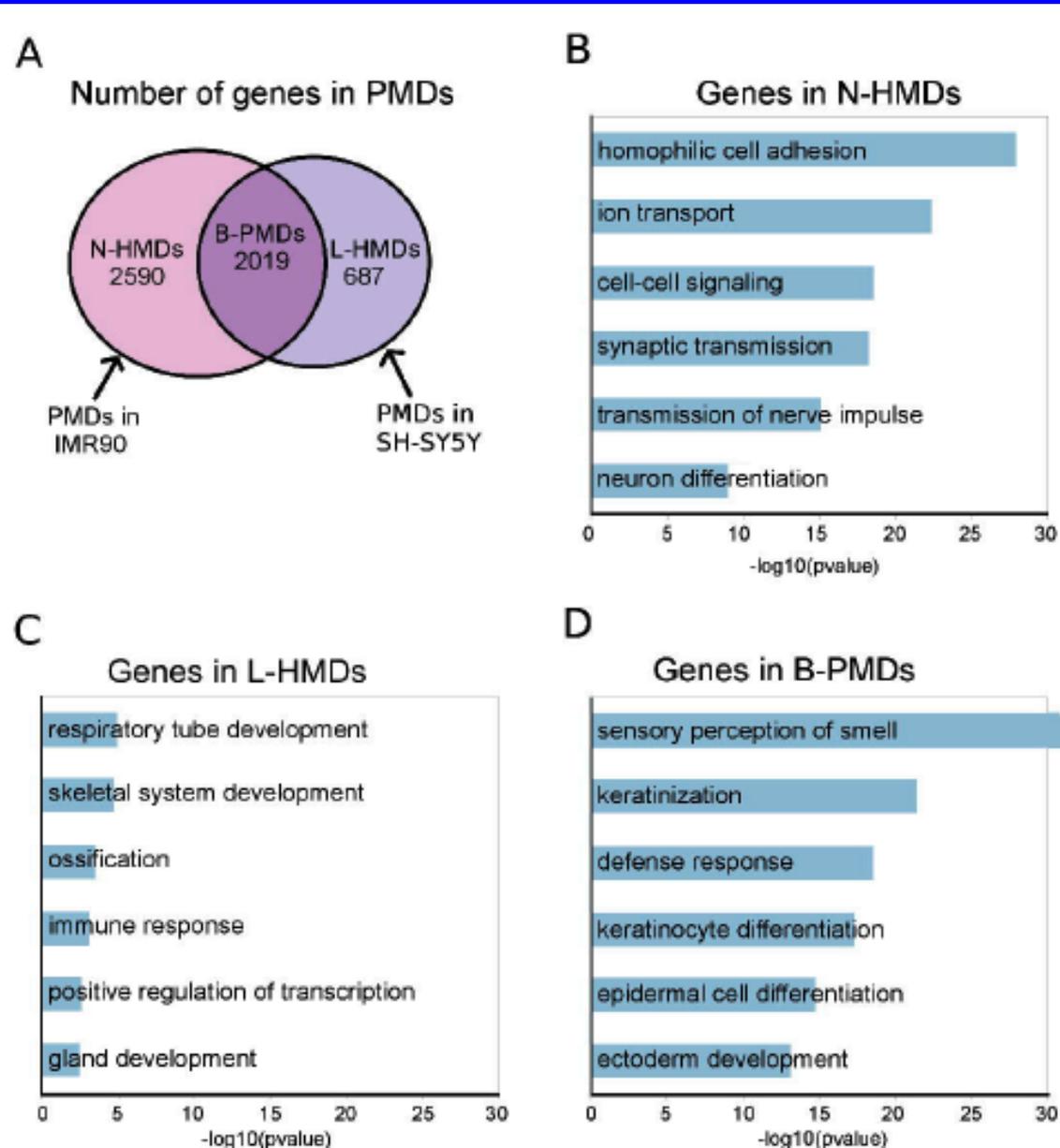
0%, 1-60%, 60-80%, 80-100% methylated

Schroeder et al, Genome Research, 2011

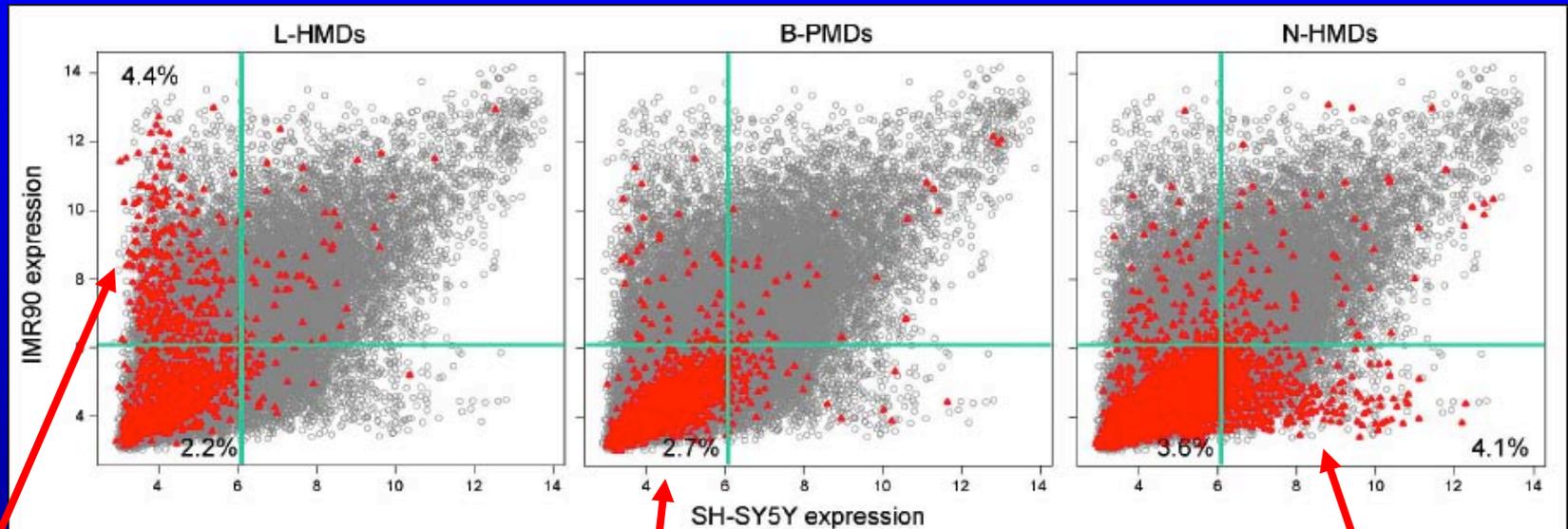


# Tissue-specific PMDs encompass neuronal genes involved in synapse maturation and neuronal differentiation

N-HMDs: neurotransmitter receptor genes, cell adhesion, Ca<sup>+</sup> signalling  
L-HMDs: developmental genes for lung, gland, skeletal, immune response  
B-PMDs, olfactory receptor gene clusters, keratin, early differentiation genes



# Tissue specific highly methylated HMDs define a subset of tissue specific genes

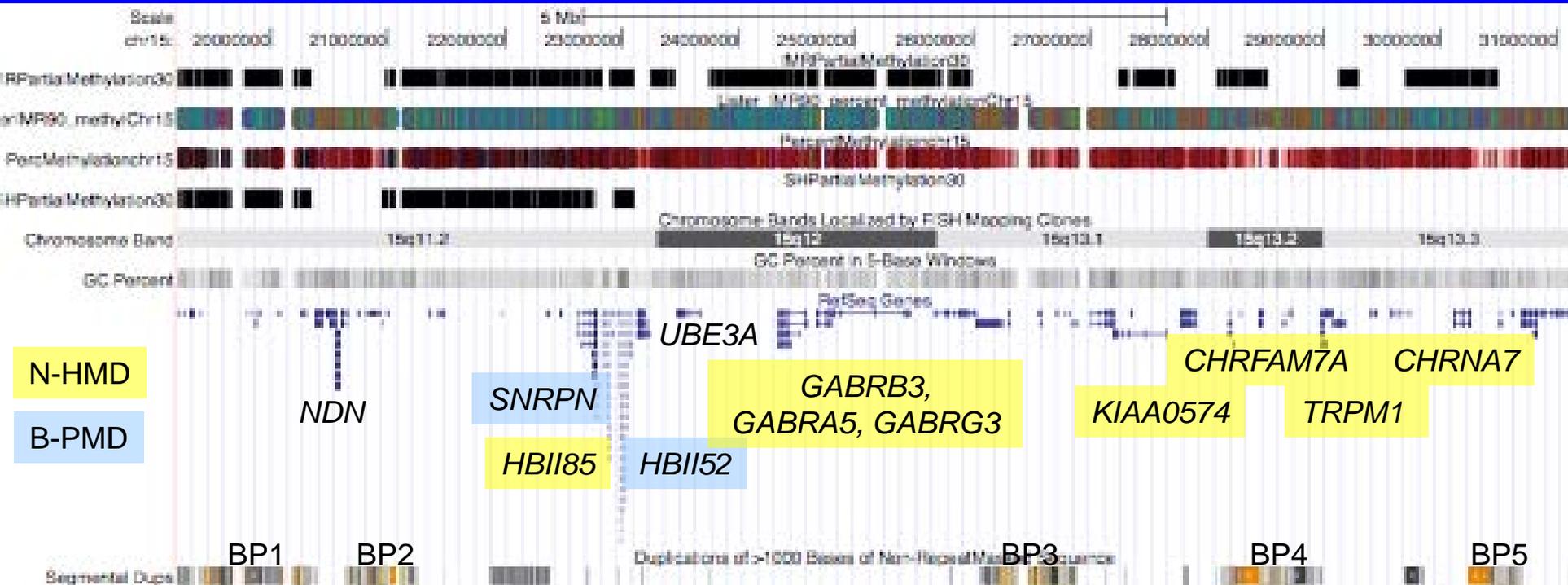


Genes in L-HMDs are expressed in IMR90 not SH-SY5Y cells

Genes in B-PMDs are mostly repressed in both cell types

Genes in N-HMDs are expressed in SH-SY5Y not IMR90 cells

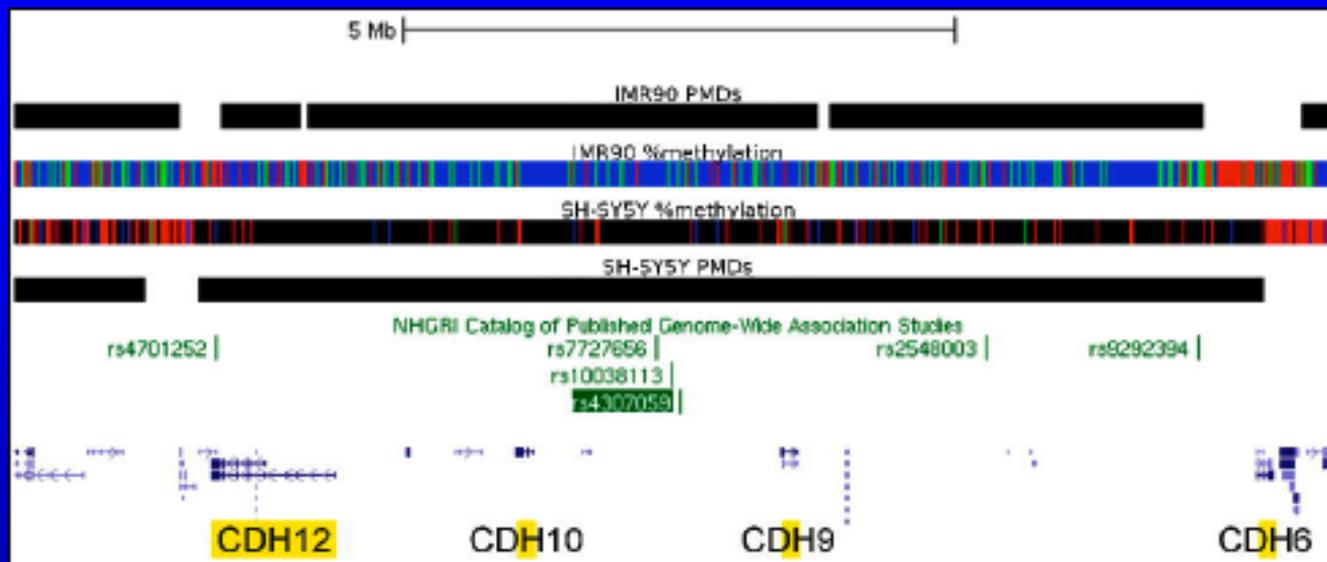
# Neuronal highly methylated (N-HMDs) and partially methylated (PMDs) domains footprint many genes on 15q11-q13



In addition to PWS and AS, copy number variations in autism, epilepsy, schizophrenia, map to this locus

# Autism genes and genetic loci are enriched in partially methylated domains

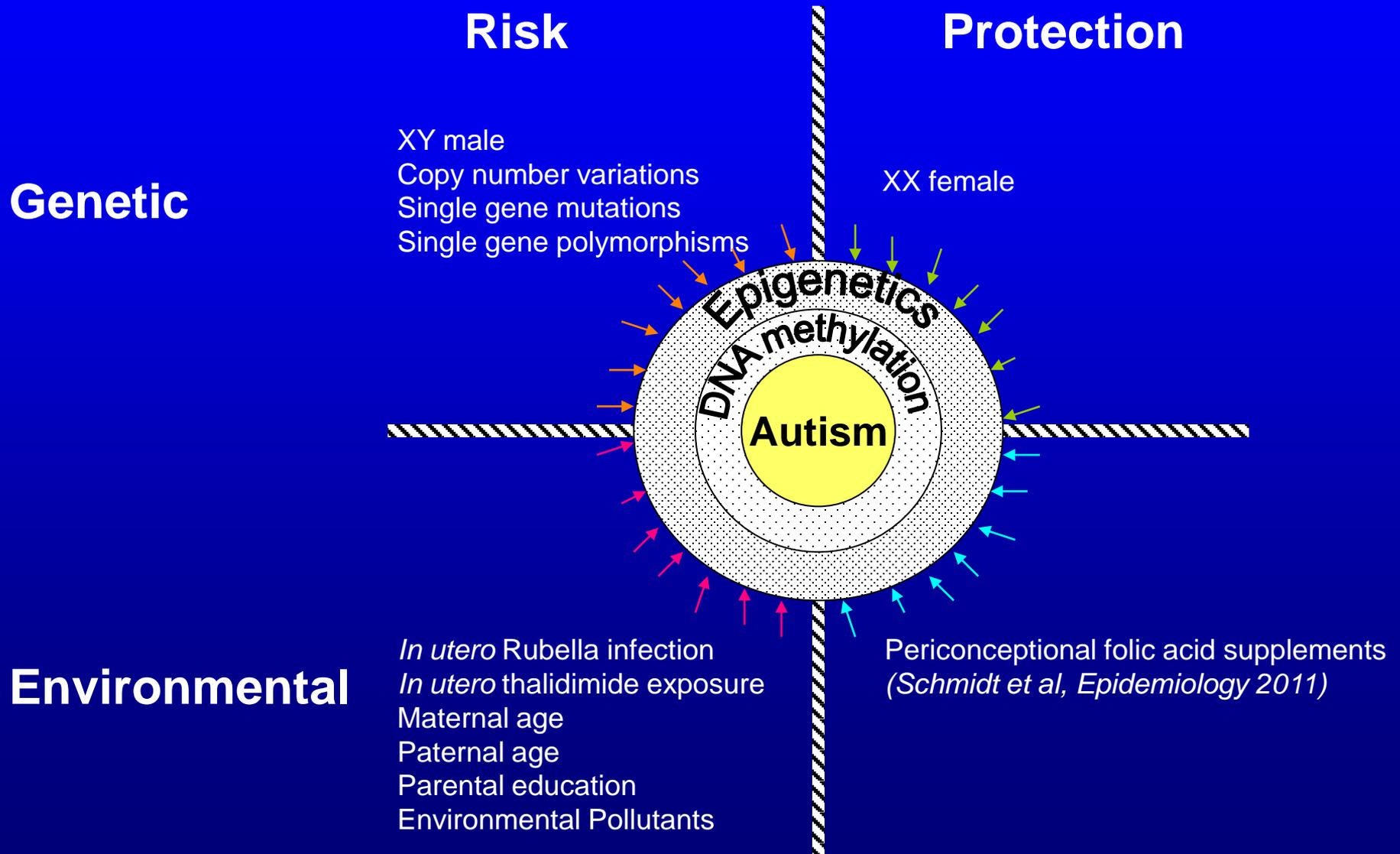
Genome-wide association study (*Wang et al, Nature, 2009*)



Autism candidate genes are preferentially enriched in PMDs

	B-PMDs	N-HMDs	L-HMDs	B-HMDs	Total genes	Chi-square
All autosomal genes in genome	2,019	2,590	687	15,140	20,436	
SFARI autism genes	17 (17.9)	49 (22.9)	14 (6.1)	101 (134.1)	181	2.01E-10
Pinto et al. autism genes	16 (12.3)	32 (15.7)	6 (4.2)	70 (91.9)	124	2.46E-05

# Epigenetic mechanisms act at the interface of genes and the environment

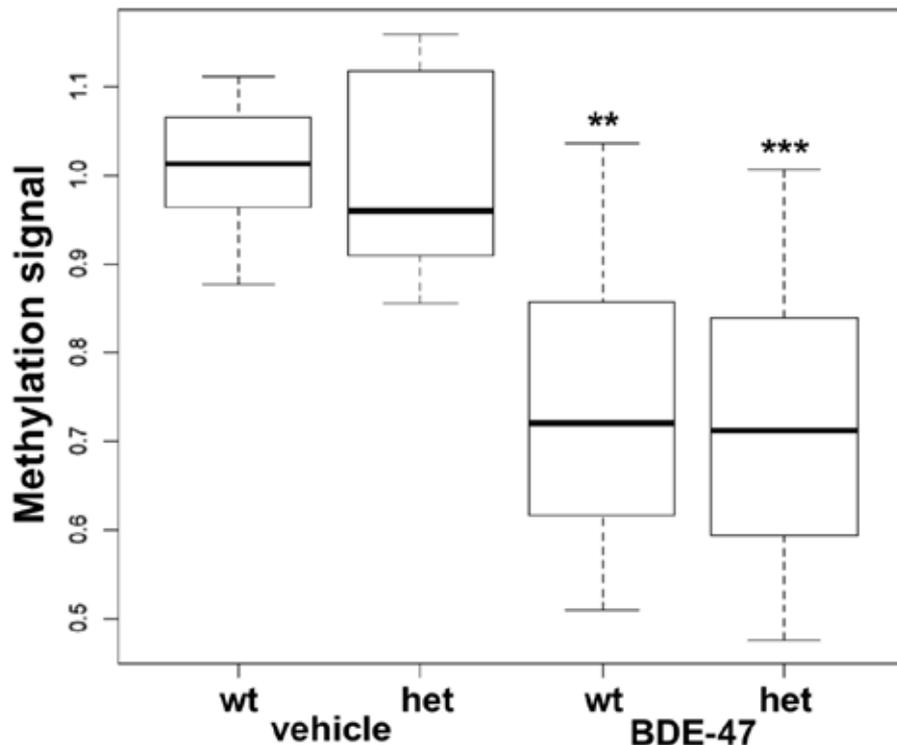


# Environmental epigenetics

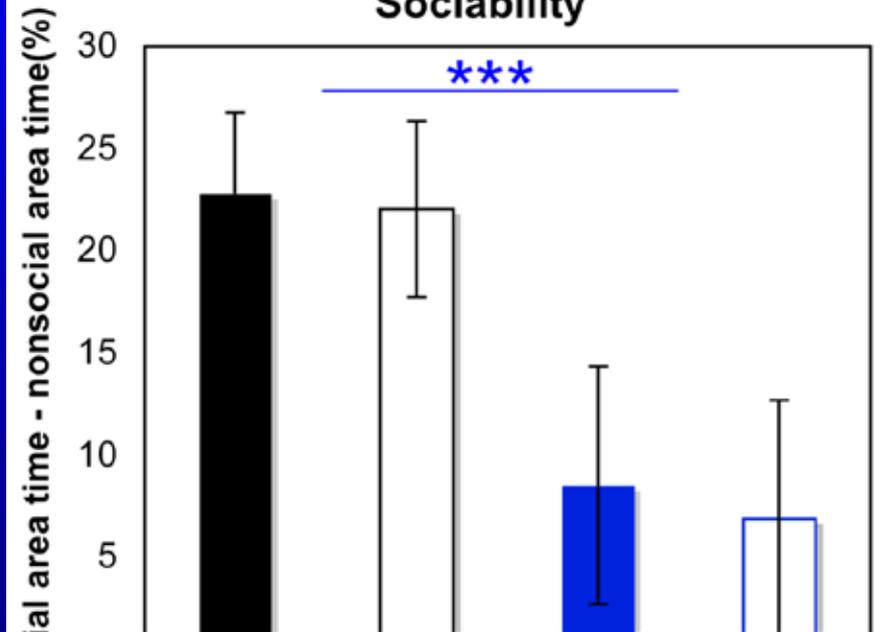
## Flame retardants (PBDEs) and social behavior

Mice perinatally exposed to BDE-47 show reduced brain global DNA methylation and reduced sociability

Global DNA methylation

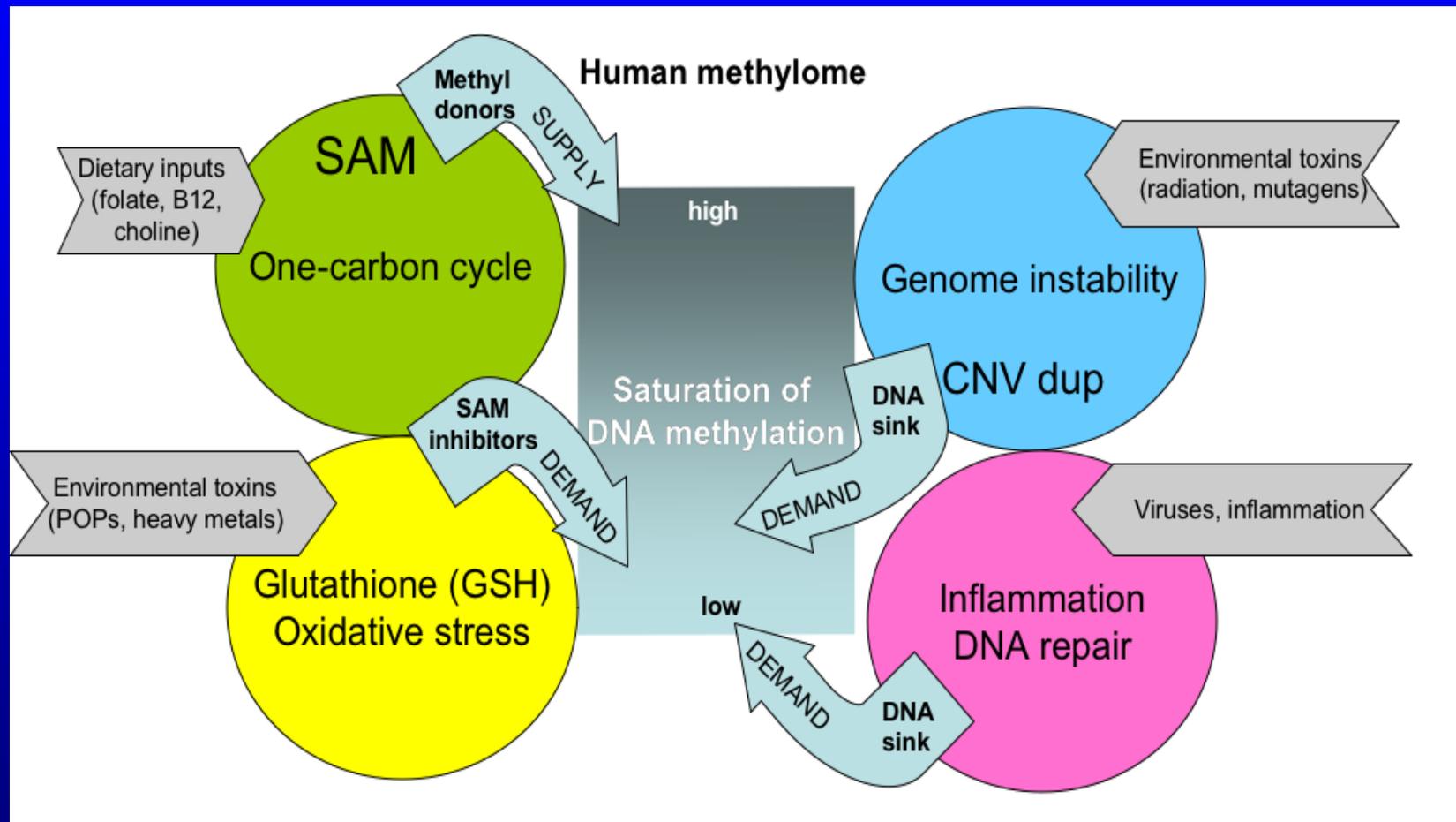


Sociability



# Environmental impacts on the brain methylome

## An integrative genomics point of view



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