

Epigenetics and multiple risk factors in development: Perspectives from autism research

Janine M. LaSalle, Ph.D
UC Davis School of Medicine



UC Davis Genome Center



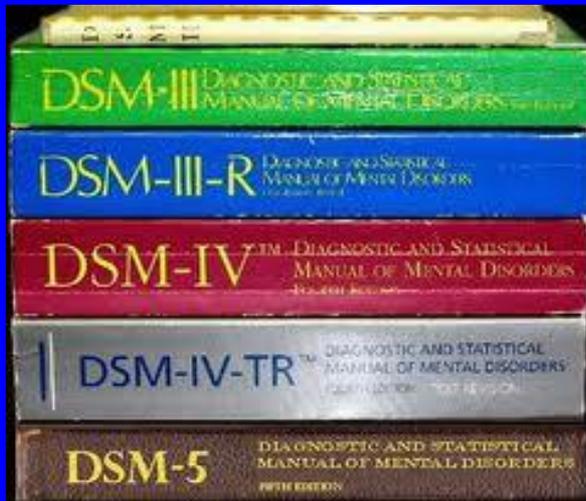
UC Davis M.I.N.D. Institute



Autism spectrum disorders



- Complex developmental disorder that usually appears in first three years of life
- Not a single disorder but a spectrum of neurodevelopmental disorders characterized by:
 - Impairments in social interactions and communication
 - Impairments in language
 - Restrictive and repetitive interests and behaviors



Challenge for research: Changing diagnoses and lack of molecular tests

DSM IV to DSM V: one heading termed “Autism Spectrum Disorders”

Genetics of autism spectrum disorders and the ongoing nature vs. nurture debate

Heritability estimates of Autism

Twins

90% based on a small monozygotic versus dizygotic twin study in 1960s (Steffenberg et al, 1989)

70-90% from a variety of larger twin studies pre-2010

38% based on 2011 study that separated calculated effect of shared in utero environment (58%) (Hallmayer et al, 2011)

Siblings

50-100x greater risk for sibs of children with autism compared to the general population

Most recent and largest family analysis from a population of 2 million in Sweden put estimate of 50% heritability, suggesting a 50% “environmental” or non-genetic component

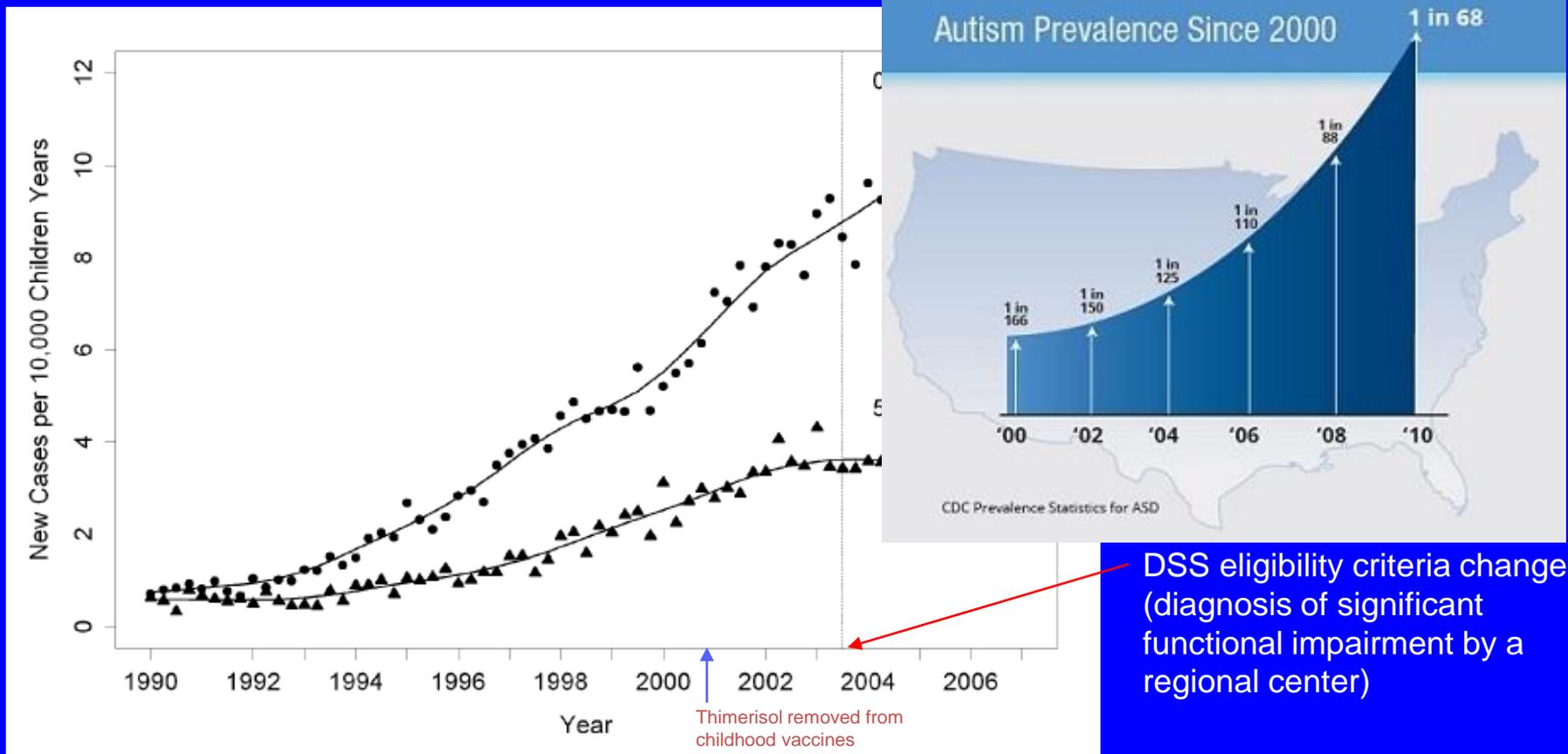
ASDs are complex genetic disorders

Multiple known genetic causes of ASD, but each contribute to at most 1% of ASDs

Is autism incidence on the rise?

California's Developmental Services System

Hertz-Picciotto and Delwiche, *Epidemiology*, 2009



Only 200% of the 600% increase can be explained by increased diagnosis

Gene x environment interactions in autism risk

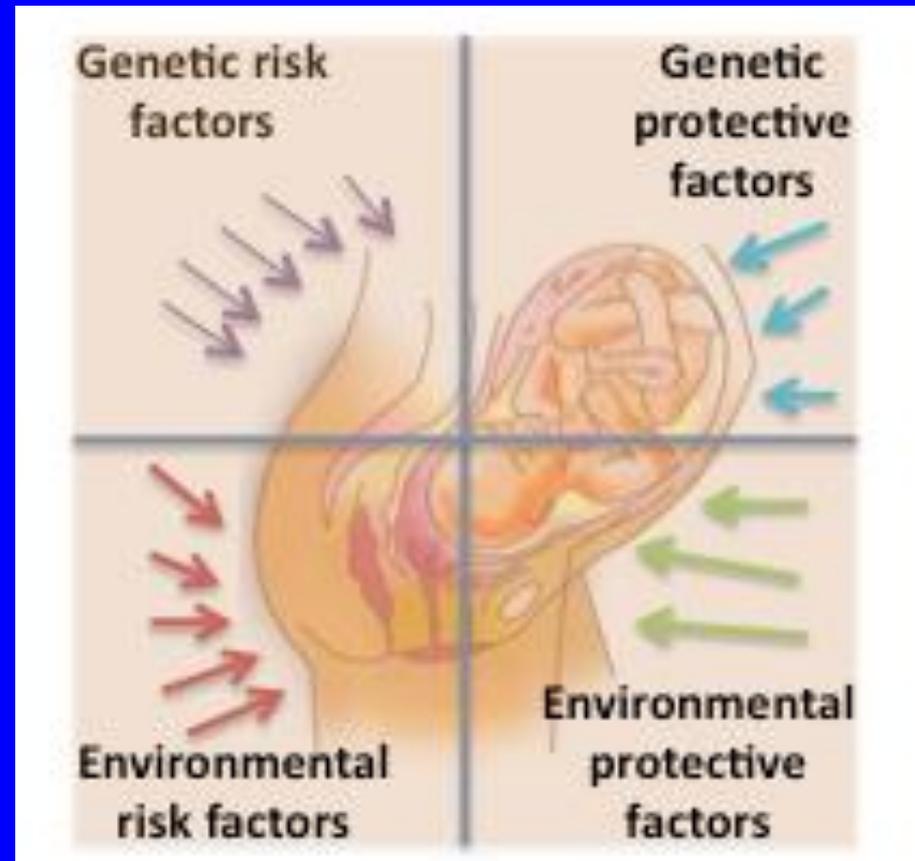
Trends Genet. March 2011 Vol. 27 No. 3, pp. 81 - 126 ISSN 0963-2688

Trends in Genetics

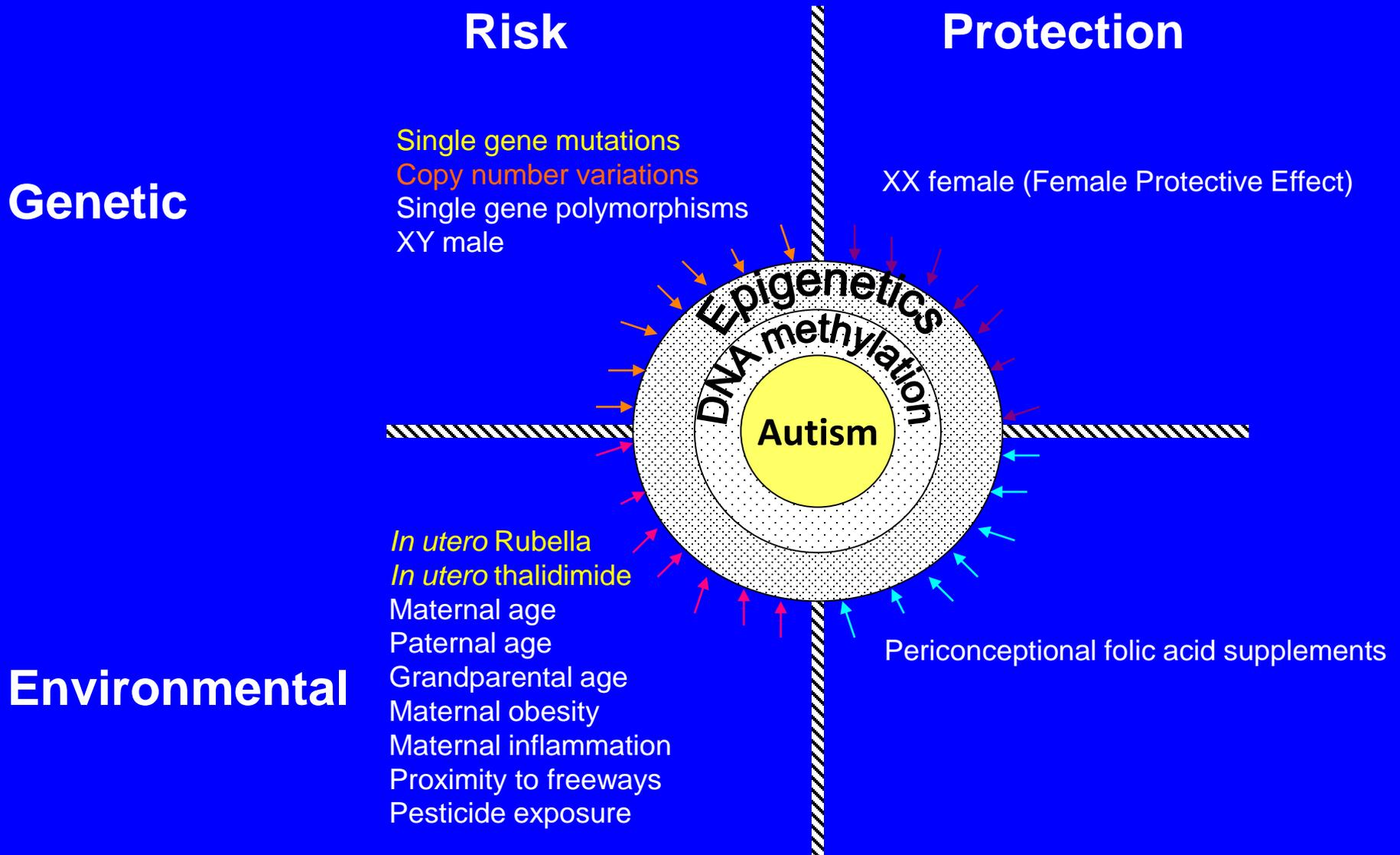


Solving the puzzle of gene-environment interactions

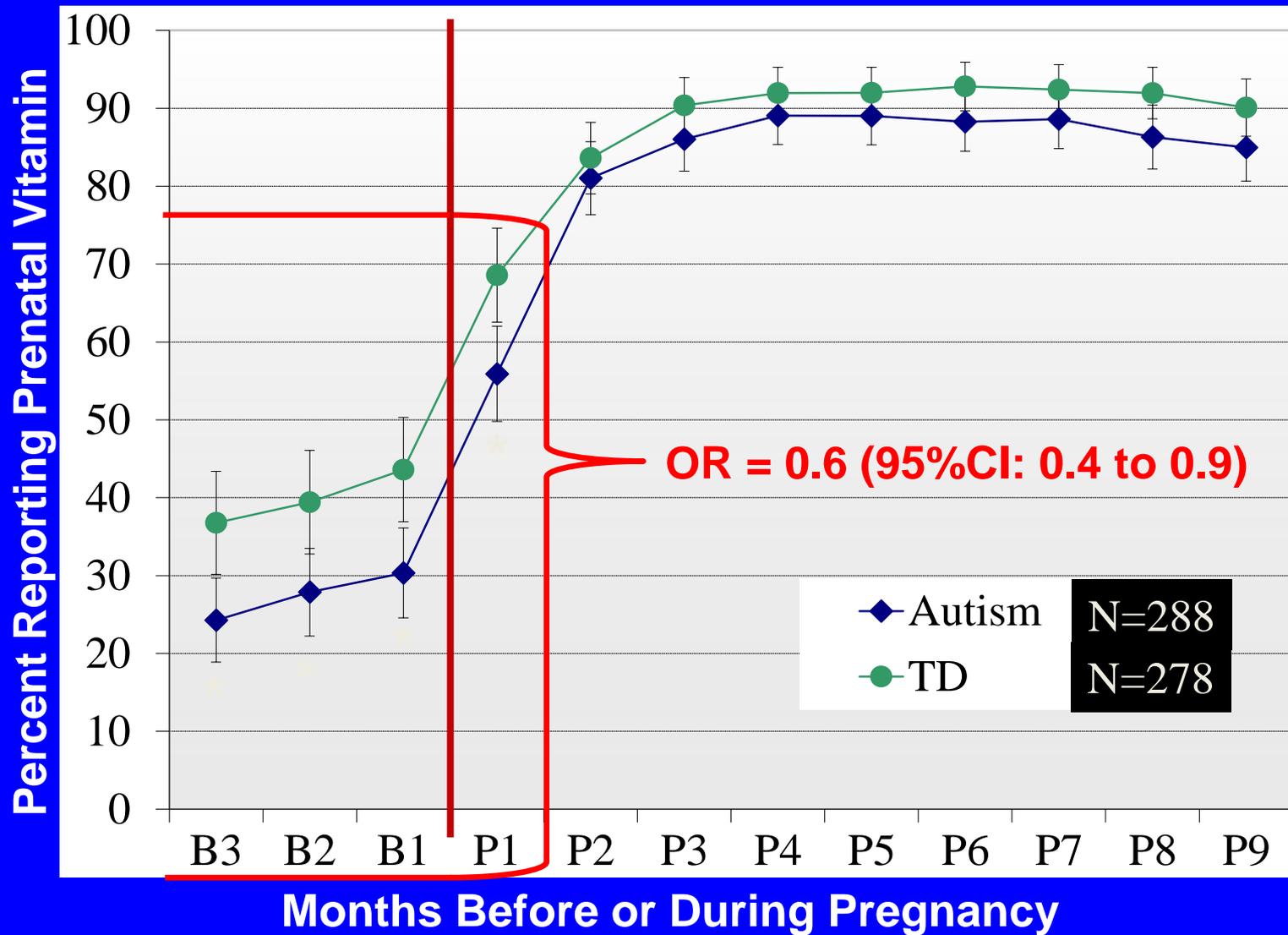
Cell PRESS



Epigenetic mechanisms act at the interface of genes and the environment



Prenatal Vitamin Use by Perinatal Month



Absence of folic acid at conception modifies autism risk with multiple environmental exposures

data from the CHARGE case-control study

Environmental Exposure During Pregnancy		800+ mcg FA Preg Month 1 aOR (95% CI)	<800 mcg FA Preg Month 1 aOR (95% CI)
Traffic-Related Air Pollution (Total Nox)	No	Reference	1.21 (0.77-1.88)
	Yes	1.25 (0.79-1.98)	2.11 (1.33-3.33)
Any Exposure to Sprays/ Foggers	No	Reference	1.41 (0.96-2.07)
	Yes	1.65 (1.06-2.55)	2.67 (1.62-4.42)
Regular Use of Sprays/ Foggers (6+ months)	No	Reference	1.39 (0.99-1.96)
	Yes	2.27 (1.29-4.00)	4.99 (2.25-11.06)
Pregnancy Chlorpyrifos	No	Reference	1.28 (0.93-2.01)
	Yes	0.75 (0.36-1.55)	2.24 (0.80-6.32)
Pregnancy Organophosphates	No	Reference	1.23 (0.87-1.74)
	Yes	0.87 (0.51-1.50)	1.89 (1.03-3.48)
Pre-conception Pyrethroids	No	Reference	1.36 (0.98-1.89)
	Yes	0.95 (0.45-2.00)	3.70 (1.23-11.13)



MARBLES

MARBLES

Markers of Autism Risk in Babies: Learning Early Signs

400 Mothers of a child with autism planning pregnancy or pregnant with another child

Recurrence rate is ~ 1 in 5 (Ozonoff et al 2011)

Pregnancy

Child Neurodevelopment

Final Dx

EEQ, FFQs

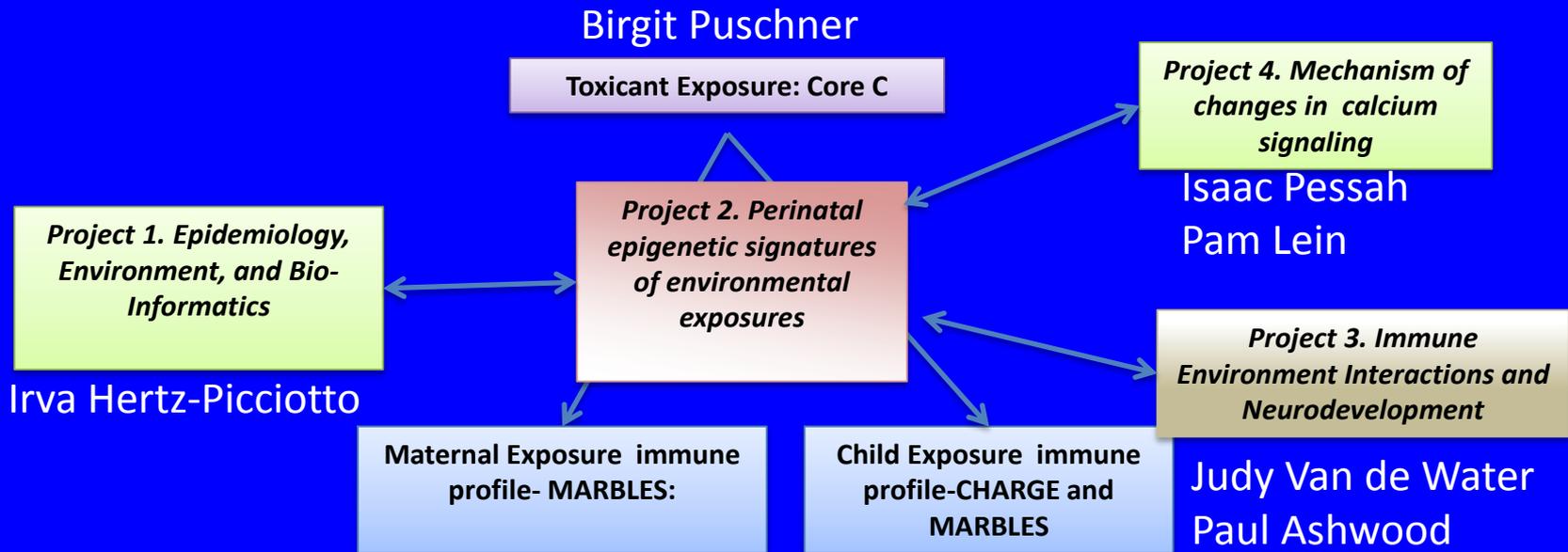
Biologic Samples

Parent Forms & Clinical Assessments



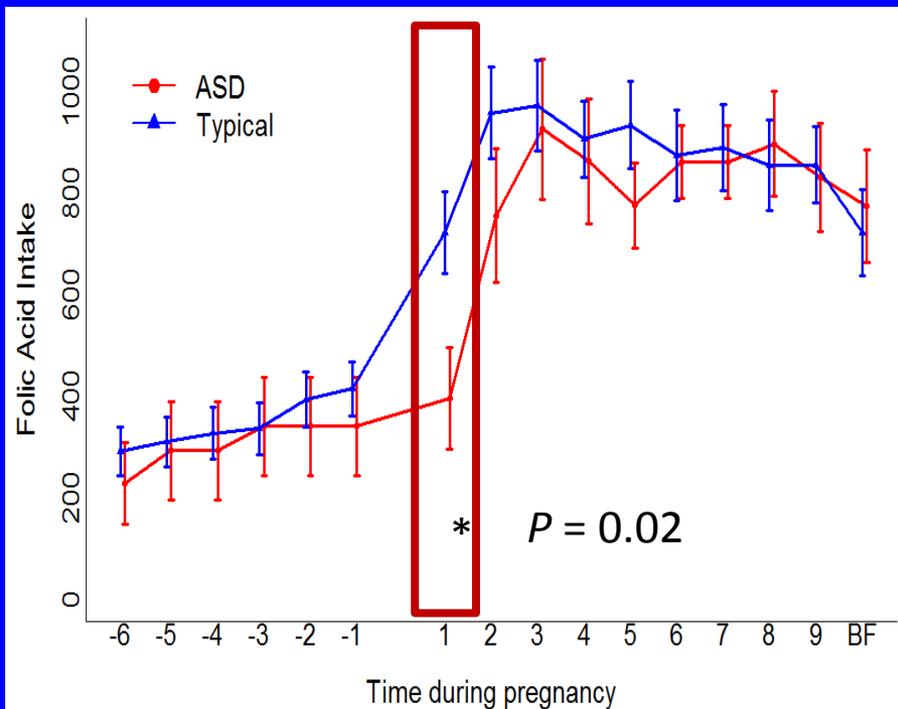


CCEH Project 2- Center interactions

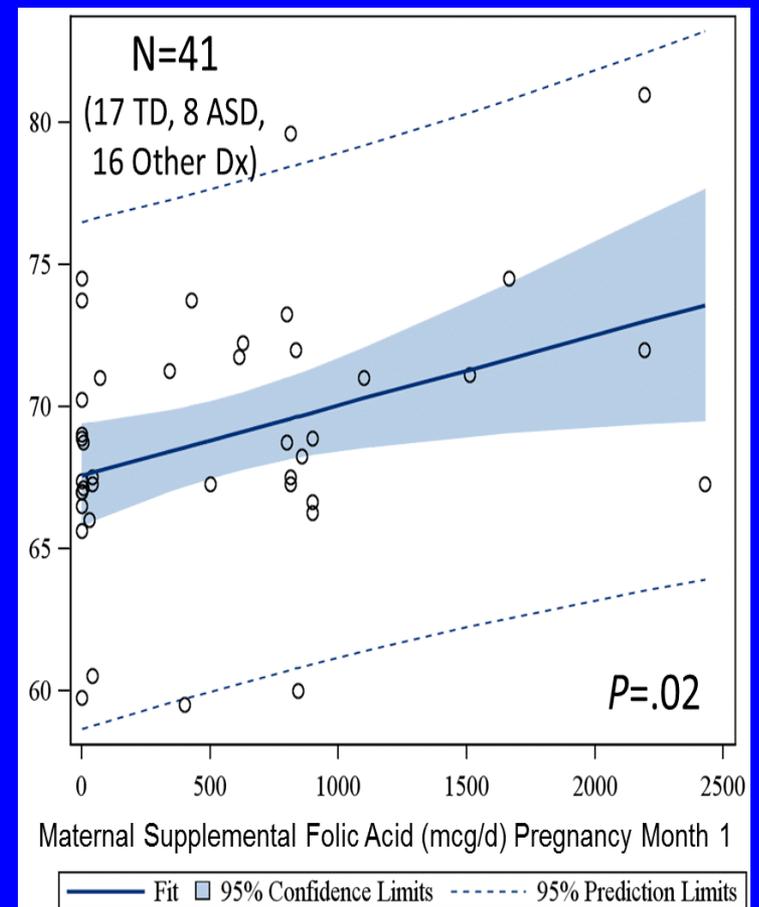


MARBLES analysis of folic acid protection and global DNA methylation

Folic Acid Intake (mcg): By Month

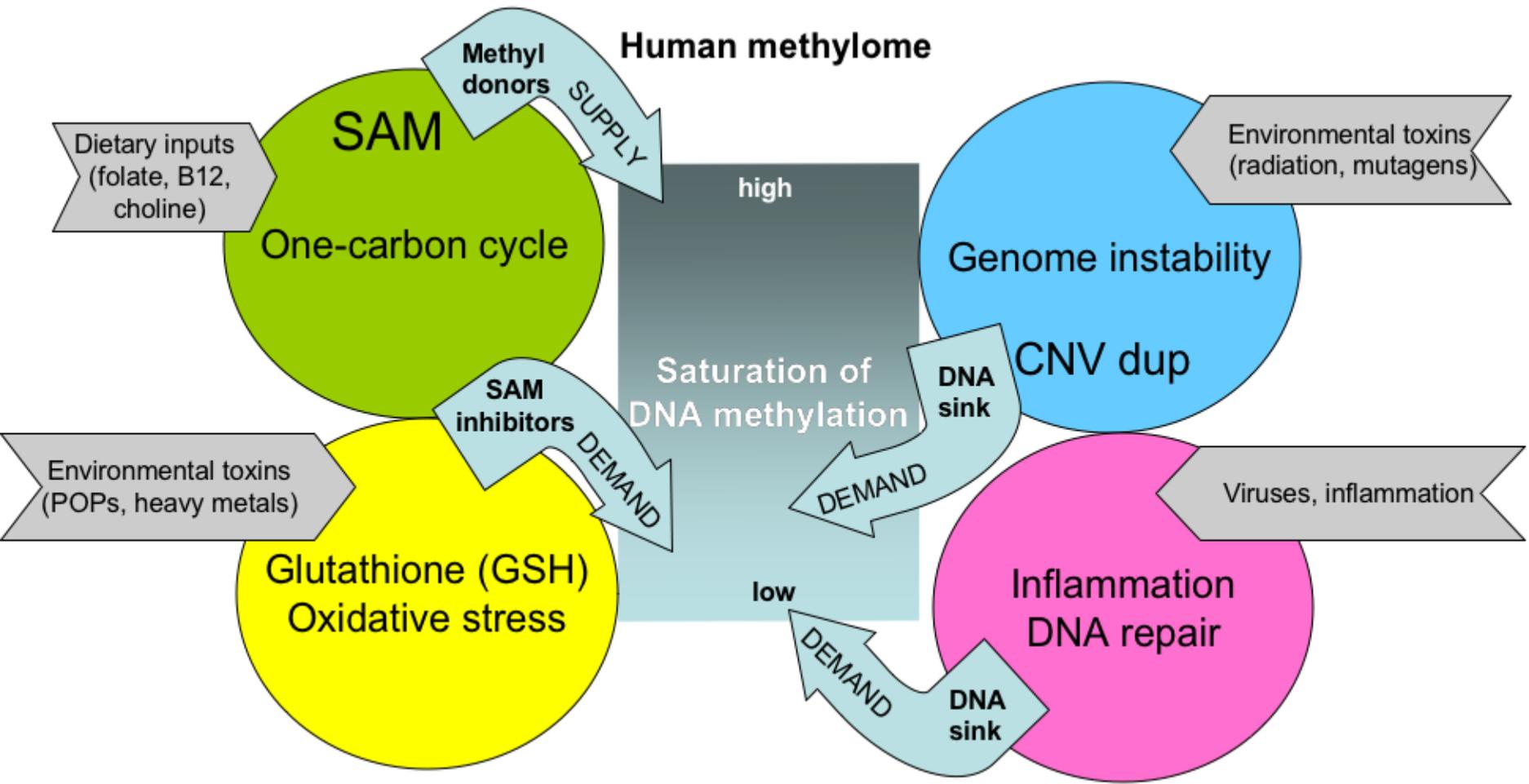


LINE1 DNA methylation by Folic Acid



Environmental impacts on the brain methylome

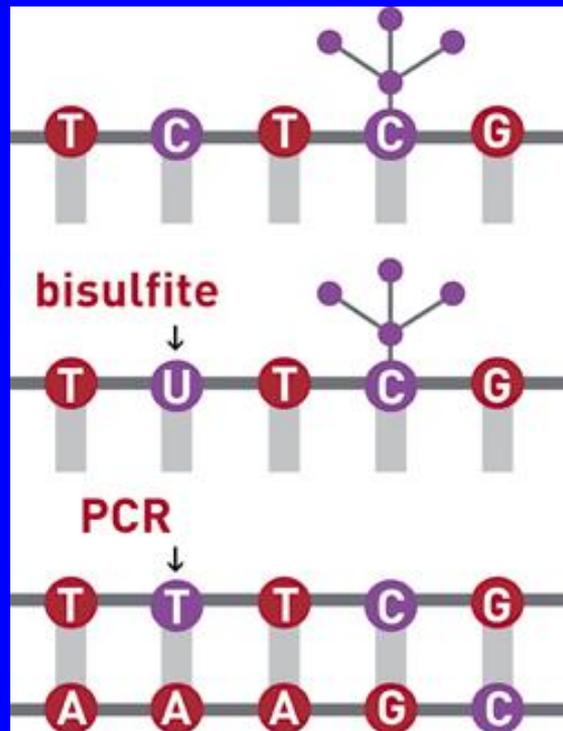
An integrative genome point-of-view



Apply genomic and bioinformatic tools to investigate MARBLES placenta and cord blood samples

- Assess the global impact on DNA methylation over partially methylated domains and repeats
- Find specific differentially methylated regions with associated with environmental exposure and/or ASD diagnosis

Methyl-C Sequencing



Acknowledgements

LaSalle Lab

Dag Yasui

Saharul Islam

Diane Schroeder

Rima Woods

Keith Dunaway

Michelle Mitchell

Weston Powell

Rochelle Coulson

Florence Crary

Justin Aflatooni

Roy Chu

Jesse Lopez

Charles Mordaunt

UC Davis Genome Center



Collaborators

Carolyn Schanen, Nemours, UDE

Jim Resnick, University of Florida

Amanda DuBose, UFL

Larry Reiter, U of Tennessee

Wendy Robinson, UBC

Paul Kostiniak, SUNY Buffalo

Doug Gillard, SUNY Buffalo

Shin-ichi Horike, Kanazawa, Japan

Makiko Megumo-Horike, Japan

Alessandra Renieri, U Siena, Italy

Marc Lalande, UCTHSC

Financial Support

NICHD, **NIEHS**, NINDS

USEPA, DOD

Brain Tissues

Jane Pickett

Autism Speaks ATP

NICHD BTB

Collaborators, UCD

Isaac Pessah

Irva Hertz-Picciotto

Rebecca Schmidt

Cheryl Walker

Robert Berman

Mari Golub

Lee-Way Jin

Izumi Maezawa

Paul Ashwood

Judy van de Water

Paul Lott

Hung On Yu

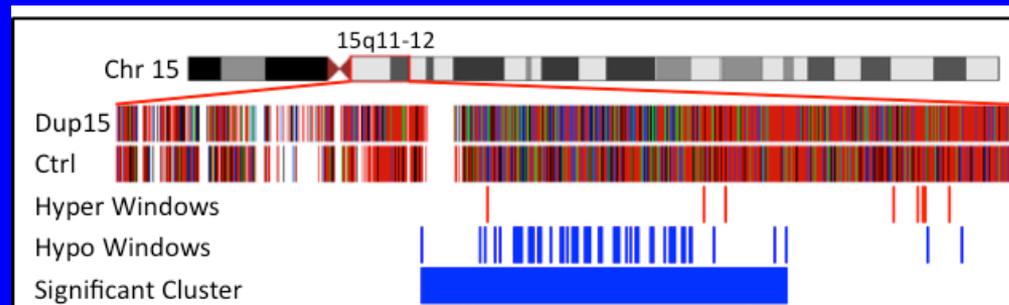
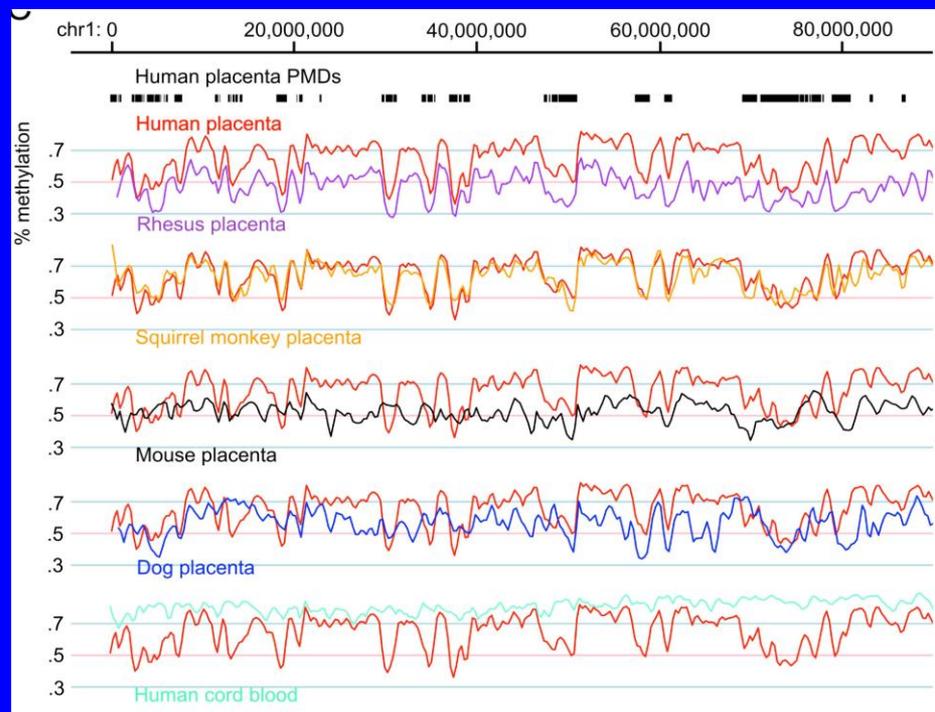
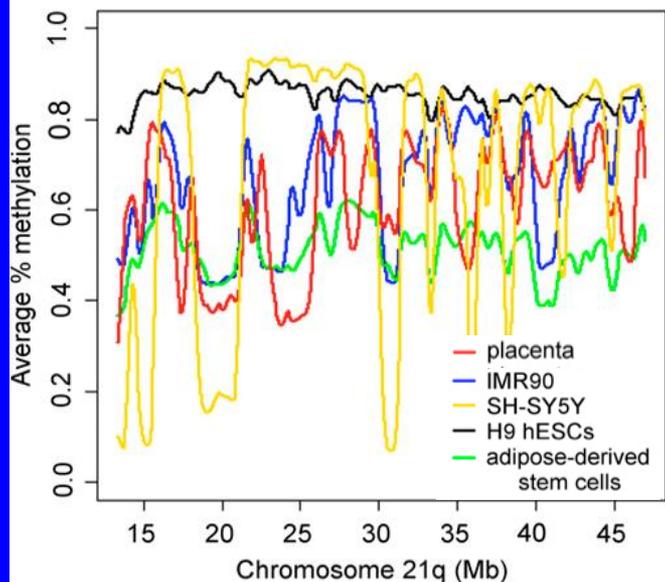
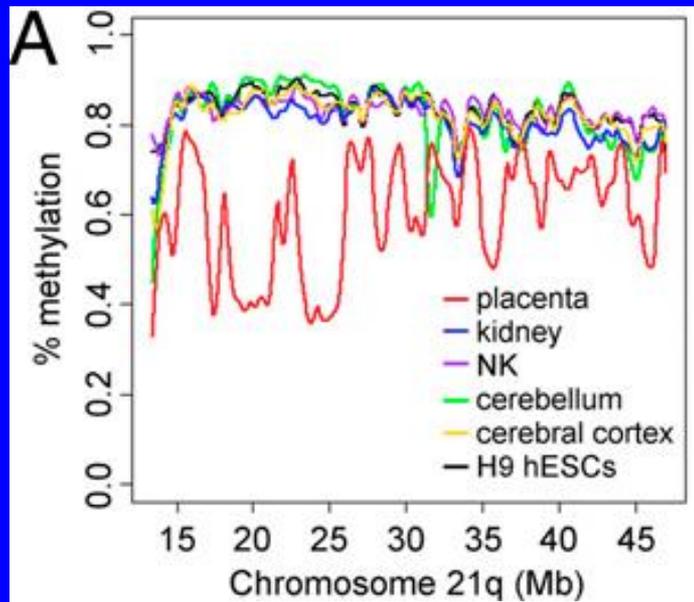
Ian Korf

UC Davis M.I.N.D. Institute



Mapping the methylome in brain and placenta

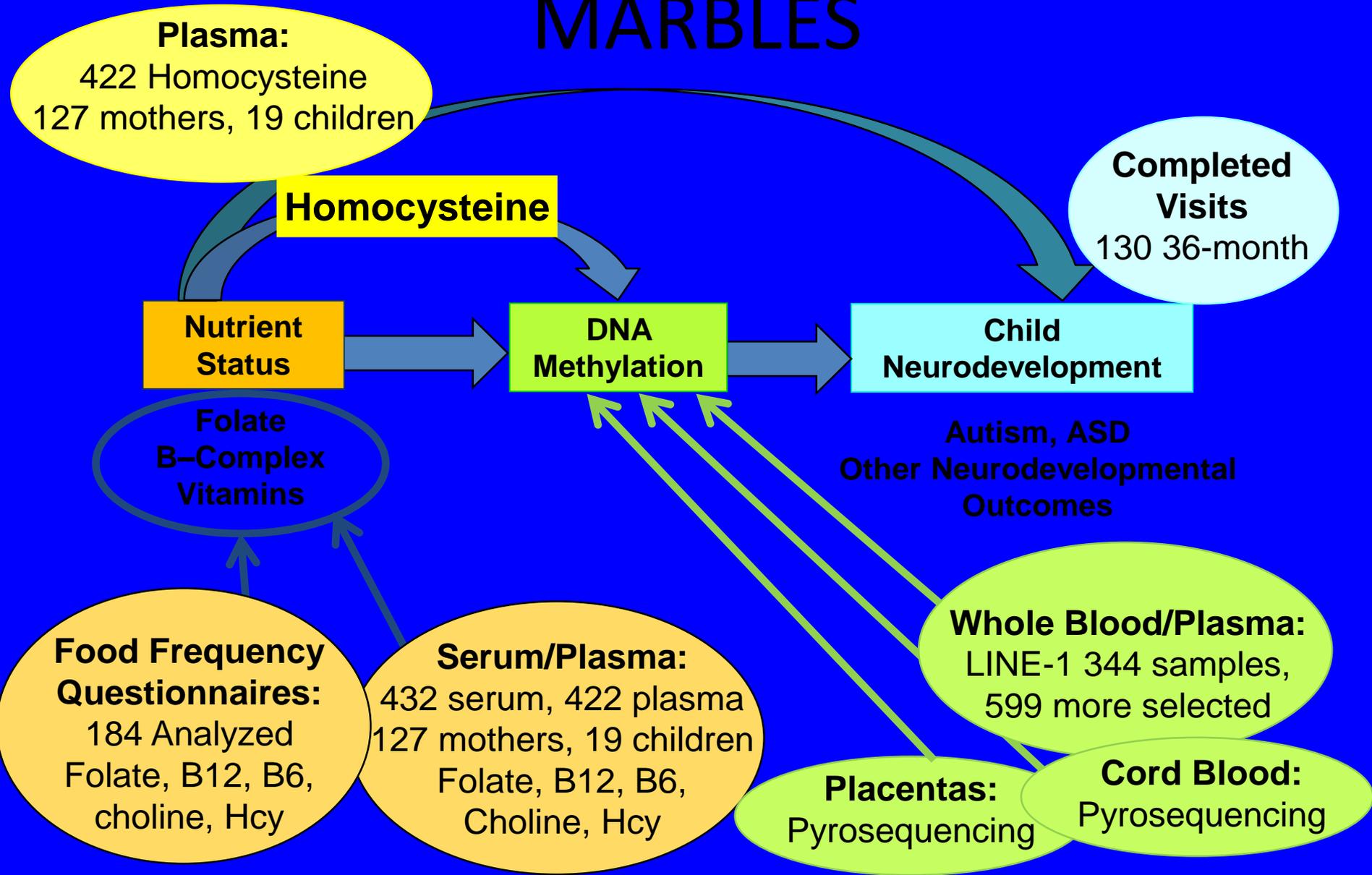
The landscape feature of partially methylated domains in early life



Prenatal vitamin protection in MARBLES

Prenatal Vitamin ≤ P1	<u>ASD</u> N (%)	<u>Typical</u> N (%)	RR (95% CI)	<i>P</i>	_{adj}RR* (95% CI)	<i>P</i>
Yes	5 (24)	42 (62)	Reference			
No	16 (76)	26 (38)	3.7 (1.5, 9.1)	.005	4.0 (1.5, 10.0)	.003

MARBLES



MARBLES

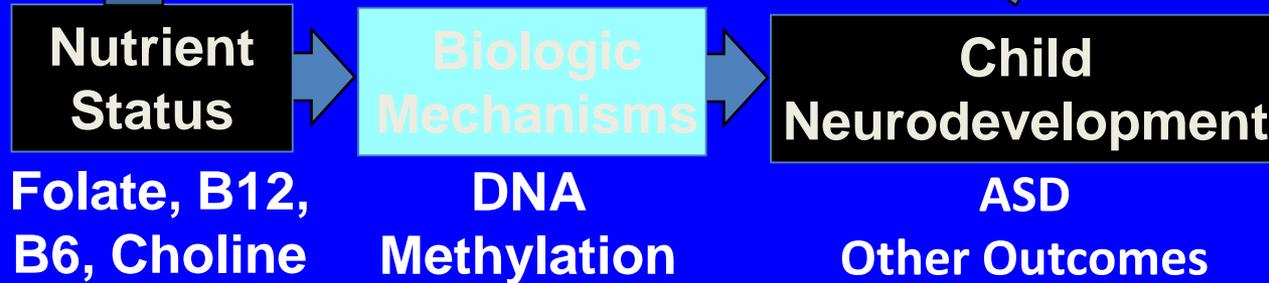
Markers of Autism Risk in Babies: Learning Early Signs PI: Irva Hertz-Picciotto

400 Mothers of a child with autism planning pregnancy or pregnant with another child

FFQs



Maternal & Child Serum



Parent Forms and Clinical Assessments

