

Epigenetics and Genomic Imprinting

IOM Workshop

Arthur L. Beaudet

abeaudet@bcm.tmc.edu

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EPIGENETICS

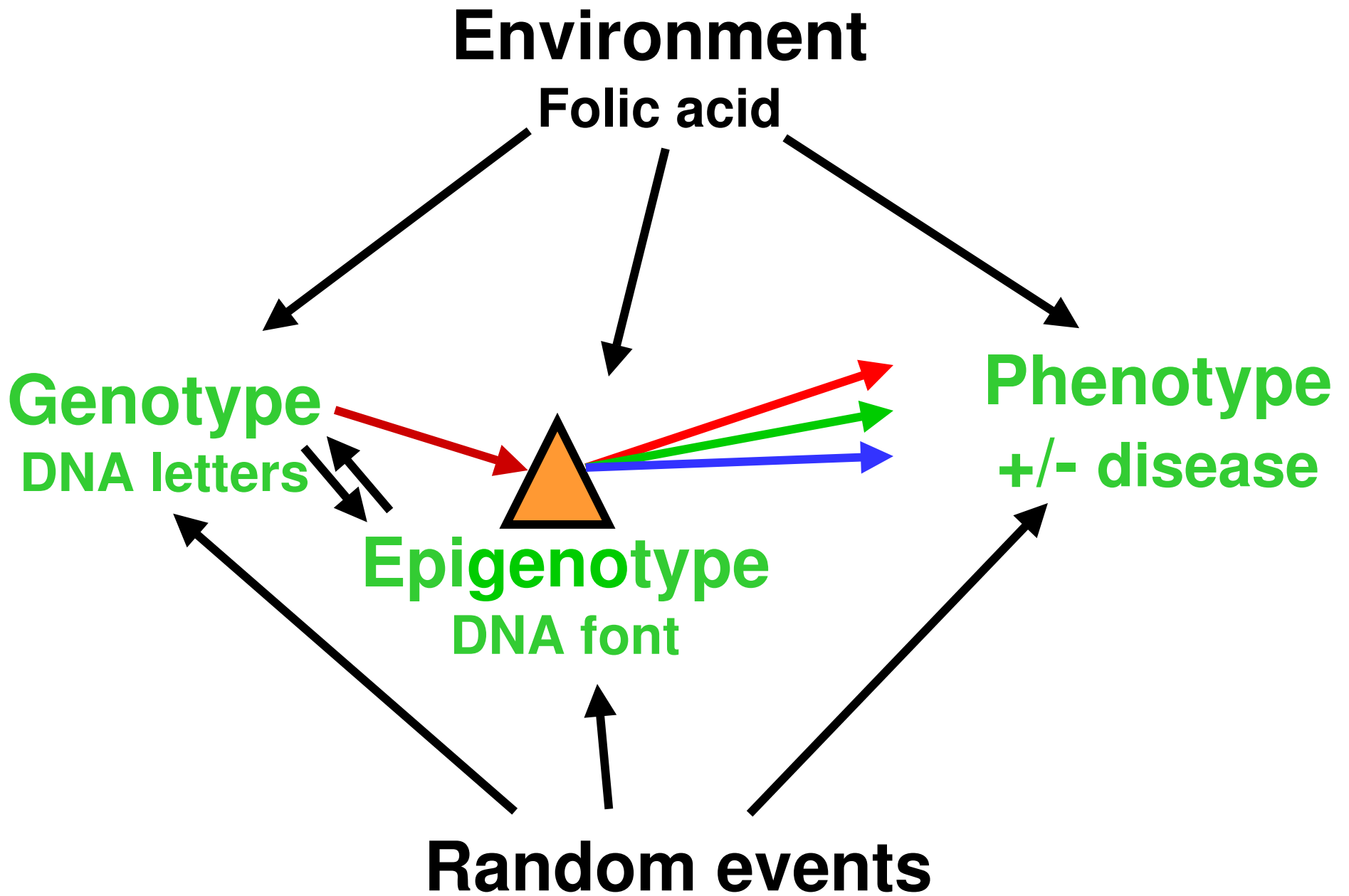
ONE DEFINITION

- The study of changes in gene function that are **stable and heritable** (or potentially heritable as in terminally differentiated neurons) and **do not entail a change in DNA sequence**.
- Not dynamic transcriptional control.
- Although epigenetic regulation is often transcriptional, some is post-transcriptional and even post-translational, e.g., prions, mad cow disease.

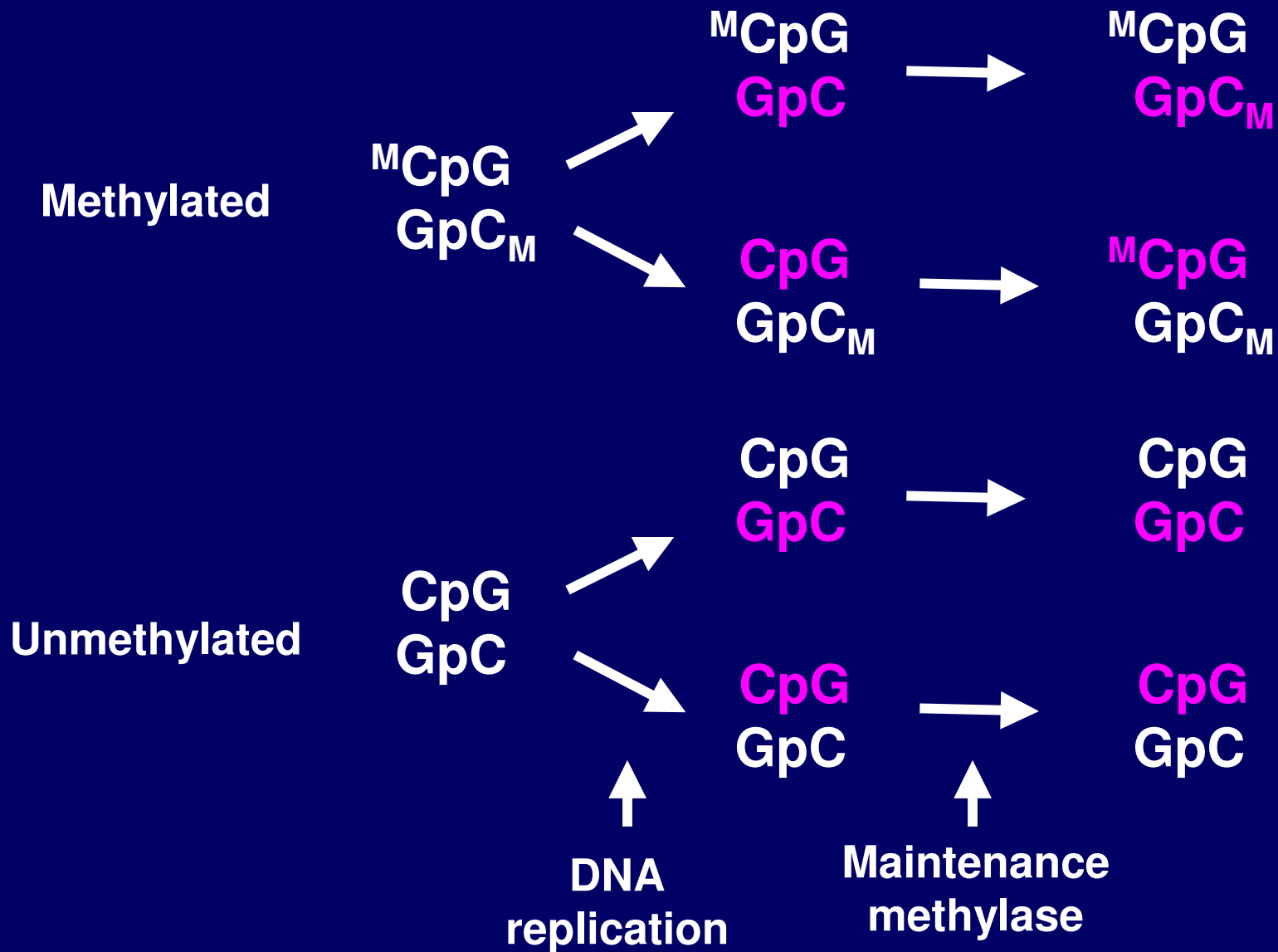
EPIGENETICS

ANOTHER DEFINITION

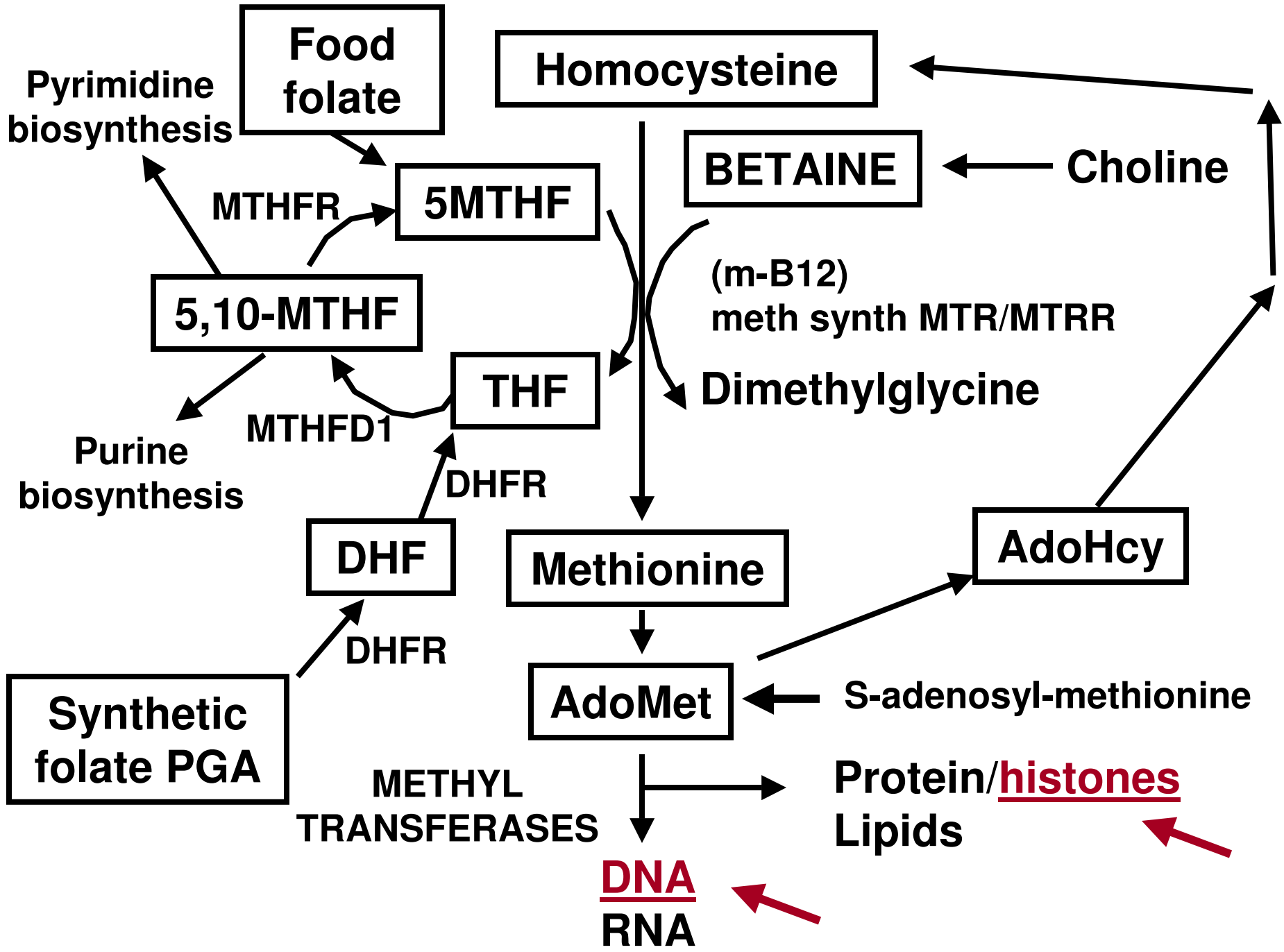
- **The adaptation of chromosome regions so as to perpetuate local activity states, whether of long or short duration and whether inherited or not.**
- **Narrower mechanistically with the focus on chromatin and the processes for its modification, but broader in terms of duration and heritability of the effects.**



DNA Methylation



FOLIC ACID AND METHYLATION AND EPIGENETICS



PGA pteroylmonoglutamic acid

EPIGENETICS AND THE HISTONE CODE

Histone tail modifications



Lysine acetylation



Serine phosphorylation



Lysine methylation



Arginine methylation

GENOMIC IMPRINTING

- An epigenetic phenomenon in which the activity of a gene is reversibly modified depending on the sex of the parent that transmits it. This leads to unequal expression from the maternal and paternal alleles of a diploid locus.

1. offspring of male donkey
2. body size and behavior
3. a very stubborn person



Hinney (foreground) vs Mule
From Pennisi, Science 293:1064, 2001

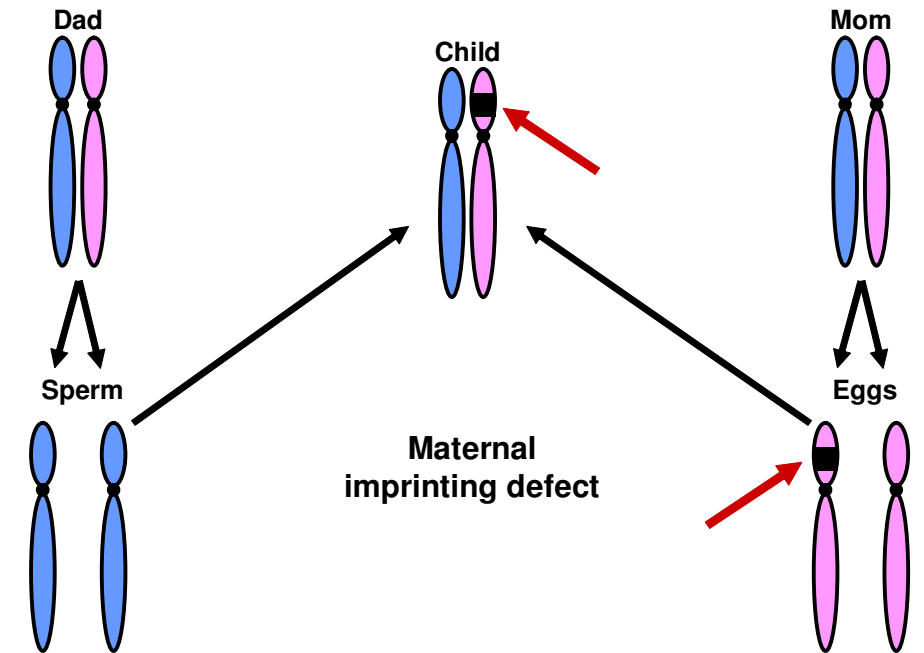
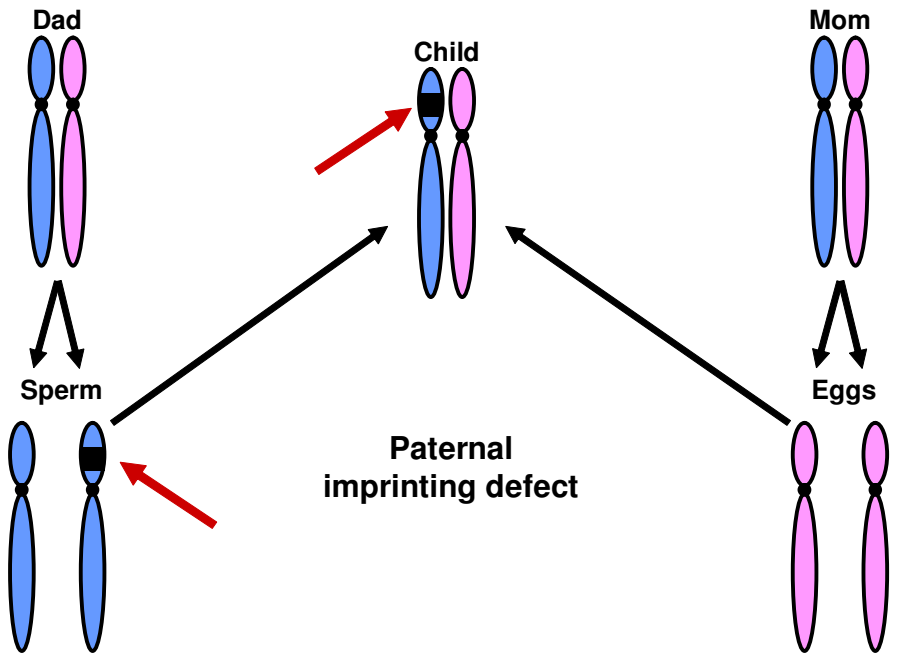
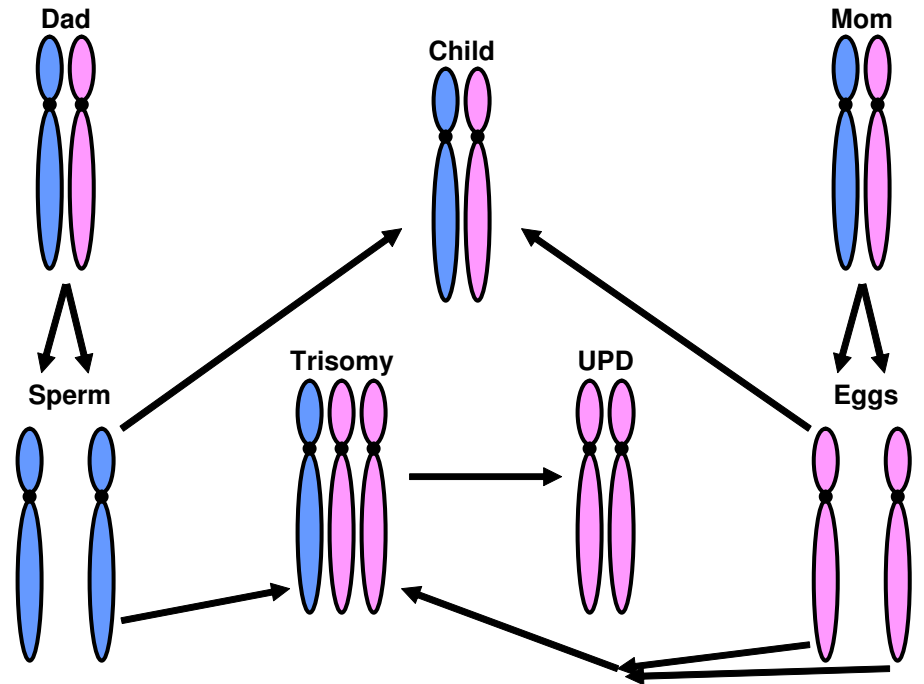
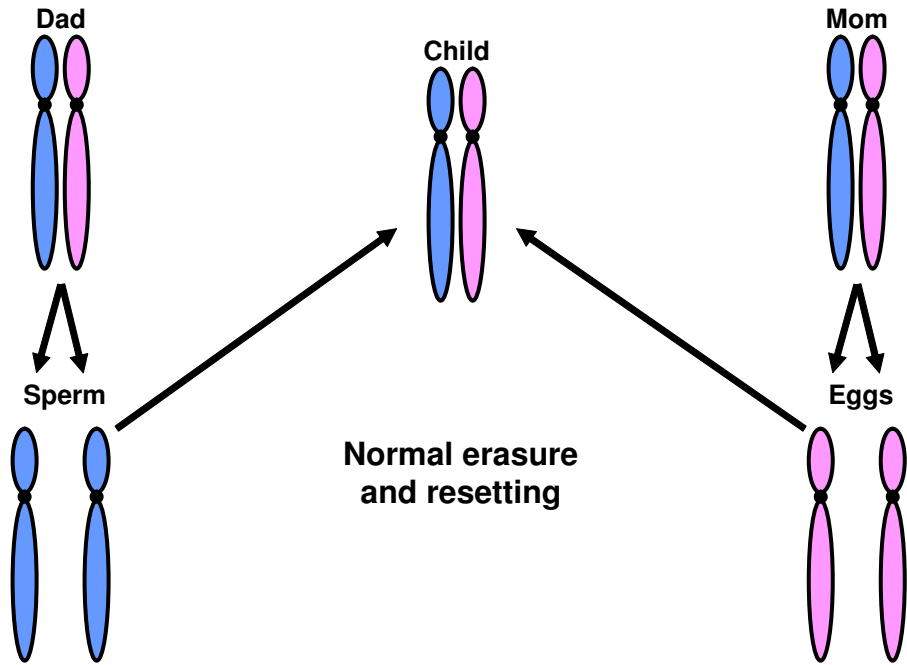
EPIGENETICS GENERALLY

- Any stable regulatory change in chromatin.
- Any change in the “font”.
- All genes involved.
- Makes a brain cell different from a liver cell.

GENOMIC IMPRINTING

- Maternal or paternal allele silenced
- Only a few genes involved.
- Mule vs hinney.

**Epigenetic control intrinsically
semi-stable**



PRADER-WILLI SYNDROME

- Infantile hypotonia & feeding problems
- Hyperphagia & obesity
- Moderate MR
- Gonadal hypoplasia
- Short stature



ANGELMAN SYNDROME

Severe learning def.

Absent speech

Happy disposition

Seizures

Ataxia / tremor

Microcephaly

Prominent mandible

Some similarities and some differences with autism



Prader-Willi

Angelman

Deletion

UPD

Deletion

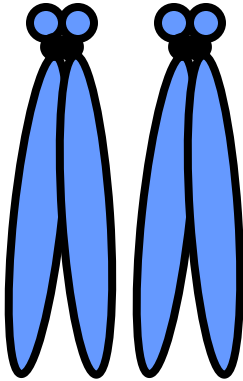
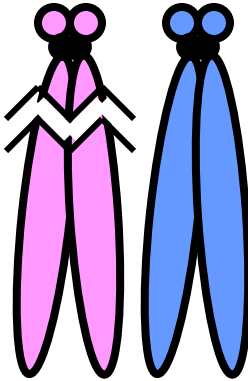
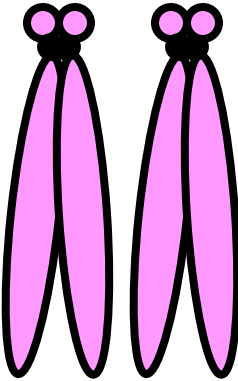
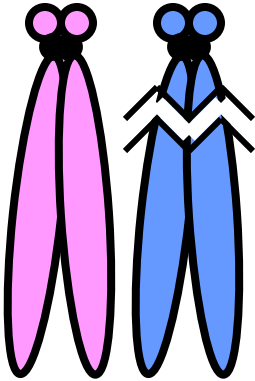
UPD

Genetic

Epigenetic

Genetic

Epigenetic



70%

30%

70%

rare

**Paternal deficiency
15q11-q13**

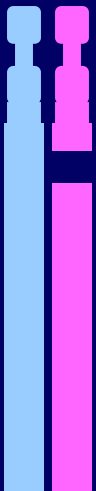

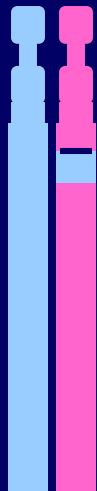


**Maternal deficiency
15q11-q13**

All deletions and UPD are *de novo* events

DISEASE DEFINITIONS

- **Genetic disease** – an aberration in nucleotide sequence causing a disease phenotype
- **Epigenetic disease** – an aberration in epigenotype (stable / heritable change in gene expression) causing a disease phenotype in the absence of nucleotide aberration
- **Both** – through altered gene expression

Angelman

de novo	de novo	de novo & inherited	de novo	de novo & inherited
Deletion	UPD	Imprint Defect IC del	Imprint Defect no IC del	<i>UBE3A</i> Null
Genetic	Epi-genetic	Mixed	Epi-genetic	Genetic
			 ICSI?	

An epigenetic defect can give the same phenotype as a genetic defect

Heterogeneity of types of defects causing one phenotype

PWS, BWS, & AHO/GNAS disorders similar

Epigenetic

De novo

**Monogenic or
oligogenic
MEGDI model**

Inherited

Genetic

**MEGDI = mixed epigenetic & genetic and
de *nov*o & inherited**

- Genetic disorders affecting chromatin & gene expression in trans
 - Rett syndrome (*MECP2*), ICF syndrome (*DNMT3B*), α -thalassemia mental retardation (*ATRX* SNF2-like)
- Genetic disorders affecting chromatin & gene expression in cis
 - Fragile X syndrome - triplet repeat expansion silencing *FRAXA*; mRNA-binding protein
 - Imprinting center deletion causing Angelman syndrome - *UBE3A* neuron specific imprinting)
- Epigenetic disorders with no nucleotide sequence abnormalities
 - Uniparental disomy
 - Imprinting defects without nucleotide mutation
 - Others? Nonimprinted genes?

CANDIDATE EPIGENETIC DISORDERS

Neural tube defects and socioeconomic cycles; deprivation at the time of pregnancy and/or when the mother was a fetus; folic acid prevention.

Schizophrenia and Dutch famine; some hints of folic acid involvement.

Autism: Some evidence for parent of origin effect. Is there an epidemic? Could folate increase risk?

QUESTIONS

Are there epigenetic diseases that involve nonimprinted genes as there are for imprinted genes?

Do epigenetic variations contribute to complex traits as they do for oligogenic traits ?

Do genome-wide genetic linkage and association studies give negative results in part because of *de novo* and epigenetic factors?

Are there adult onset epigenetic diseases?
Obesity, type II diabetes,
hypertension?

AUTISM

Facts: High "heritability" judged by MZ twins; MZ >> DZ concordance; lack of Mendelian inheritance; and failure to find strong evidence of genetic linkage or association

Common interpretation: Large number of loci (10-15) with inherited genetic (nucleotide sequence based) effects and therefore detectable in leukocyte DNA

Alternative interpretation: Oligogenic with major *de novo* contributions of genetic or epigenetic nature and possibly brain-specific; *de novo* could explain twin data

AUTISM HYPOTHESES AND ASSUMPTIONS

Fact: Sex ratio M:F of $\gg 4:1$

Common interpretation: Sex-limited effects on autosomal loci

Alternative interpretation: A major gene on the X or Y chromosome

High concordance MZ twins but low in DZ suggests de novo factor

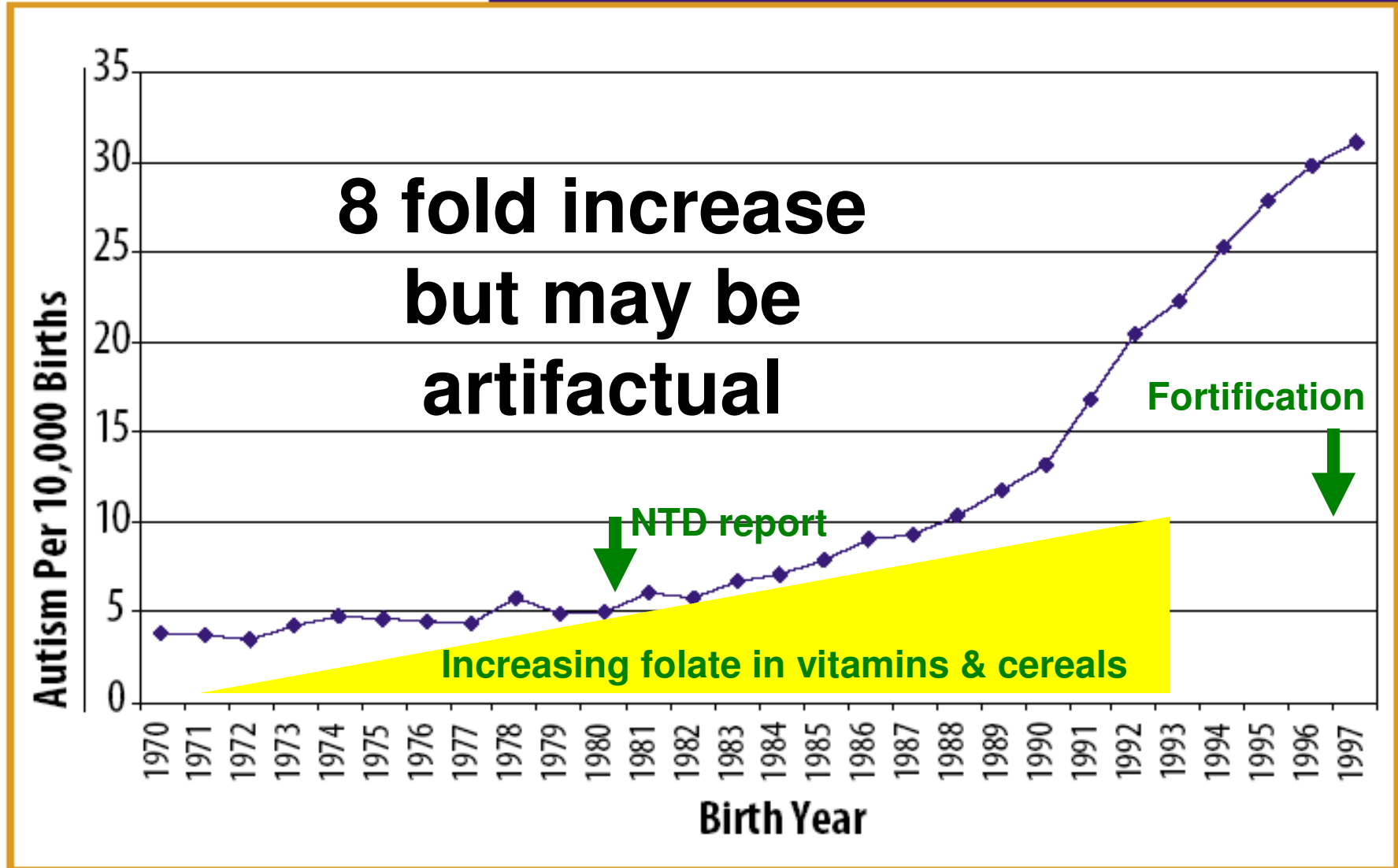
Disorder	MZ	DZ
Down syndrome	100%	<5%
Achondroplasia and Rett de novo	100%	nil
Autism narrow	~60%	nil
Autism broad	~90%	~10%
De novo gametic or preMZ imprinting defect	100%	<5%

Angelman

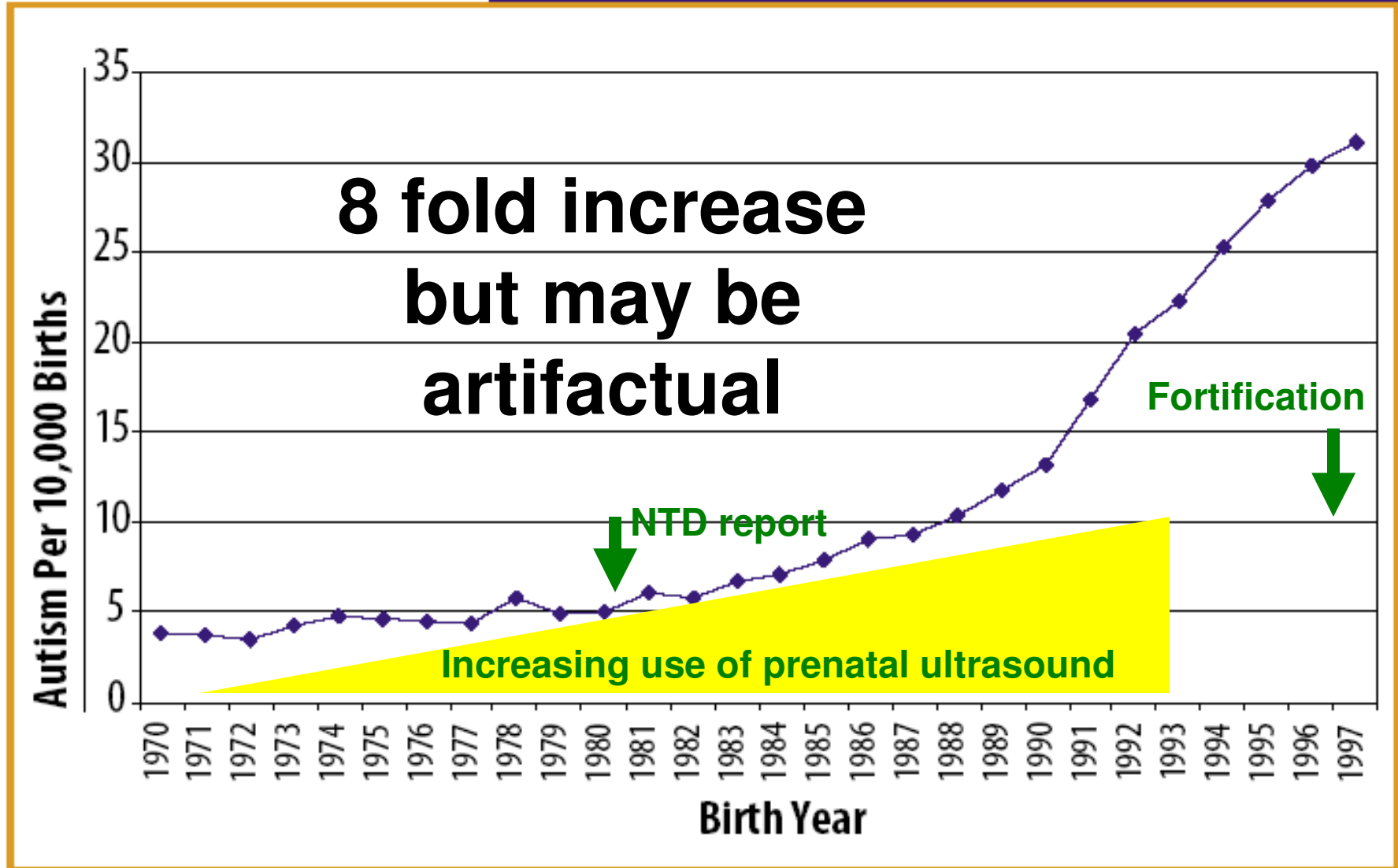
Autism?

Deletion	UPD	Imprint Defect	<i>UBE3A</i> Null	Interst dup	Isodi-centric	Other paternal imp?	Other maternal imp?	Other gene ?
Genetic	Epi-genetic	Mixed	Genetic	Genetic	Genetic	Mixed?	Mixed?	Mixed?
		ICSI				?	?	Frequent?

**Figure 3 - Uncorrected Birth Year
Prevalence Rates from 1970 through
1997 for the 2002 Population of
Persons with Autism (Codes 1 & 2)**



**Figure 3 - Uncorrected Birth Year
Prevalence Rates from 1970 through
1997 for the 2002 Population of
Persons with Autism (Codes 1 & 2)**



PREVALENCE OF SUPPLEMENT USE IN USA

- NHANES I (1971-74) --- 23 %
- NHANES II (1976-80) --- 35 %
- NHANES III (1988-94) --- 42 %
- Through 1999 --- ~40 %
- **VITACREST**; 1972; 0.1 mg folic acid
- **1973**; OTC limit raised to 0.4 mg folic acid
- **ONE-A-DAY**; none to 1976; then 0.4 mg
- **VIDAYLIN**; none to 1977; then 0.4 mg

FRAMINGHAM OFFSPRING STUDY

	Number 756	Plasma folate ng/ml	
		1991-1994	1995-1998
No B vitamin supplements	553 (73 %)	4.6 (4.4-4.8)	4.8 (4.6-5.1)
B vitamin supplements	203 (27 %)	11.4 (10.5-12)	14.1 (13.1-15.2)

Jacques et al. PMID 10320382

Low folic acid

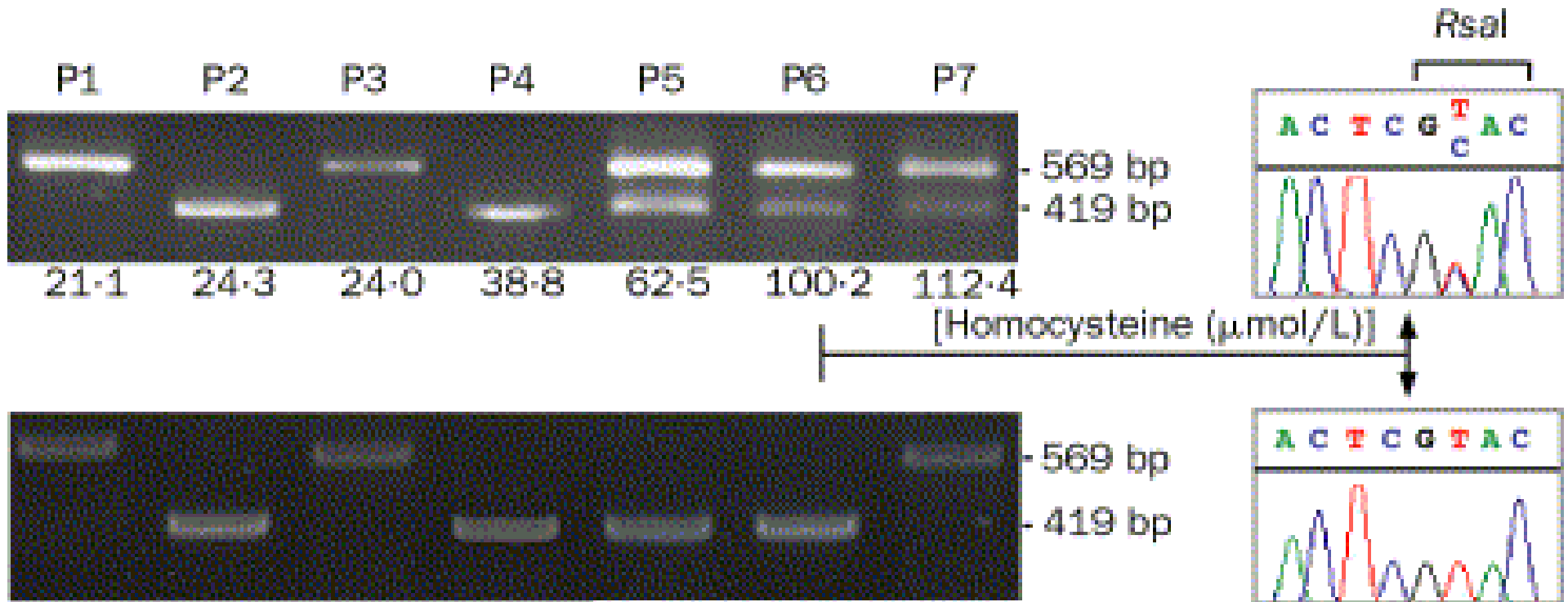
High folic acid

methylation



**Wolff *et al.*, *FASEB J* 1998;
12:949-957**

Top folate deprivation; bottom folate supplementation



Monoallelic vs biallelic expression of H19

Folic acid changes imprinted gene expression

FOLIC ACID AND GENES

- **Folic acid definitely changes the action of some genes, probably especially imprinted genes**
- **The folic acid intake of the population at large and particularly reproductive age women has been dramatically increased over the last three decades**

CANDIDATE FACTORS FOR POSSIBLE INCREASE IN AUTISM

- Childhood vaccines
- Thimerosal
- Prenatal ultrasound, Pasko Rakic unpublished data
- Antenatal steroids
- Epidural anesthesia
- Magnesium sulfate
- Maternal/paternal age

MORE CANDIDATE FACTORS FOR POSSIBLE INCREASE IN AUTISM

- **Management of preterm labor**
 - **Terbutaline toxicity in rats**
- **ART/ICSI & cryopreservation of embryos; ICSI and imprinting defects causing AS and BWS**
- **Folate**, vitamins, diet
- **Postnatal differences**

**Your folate level (and
imprinted gene expression?)
are different today than they
were 15 years ago!**

**We need to know more about
whether folic acid intake is
increasing or decreasing the
incidence of any diseases!**

There is an urgent need to know if the incidence of autism has increased, and if so what has caused the increase.

I am not convinced that the CDC is doing enough to address these questions.

END

- abeaudet@bcm.tmc.edu for copy of
Powerpoint

RECOGNITION

Present lab

Trilochan Sahoo

Xinna Zhang

Yong-hui Jiang

Marwan Shinawi

Scott Dindot

Jan Bressler

Shay Ben-Shachar

South Carolina Autism Project (SCAP)

Roger Stevenson et al.

Microarray analysis

Chad Shaw

AGRE

NIMH/Stanford

Autism Tissue Program

Harvard / NIH Brain
Banks

Report to CA legislature

M.I.N.D. Institute Oct. 17, 2002

- **Without evidence for an artificial increase in autism cases, we conclude that some, if not all, of the observed increase represents a true increase in cases of autism in California, and the number of cases presenting to the Regional Center system is not an overestimation of the number of children with autism in California.**
- **<http://www.dds.cahwnet.gov/autism/mindreport.cfm>**

Fombonne JAMA

Jan. 2003 / PMID 12503982

- **“Therefore, from available evidence it can be concluded that recent rates for both ASD (autism spectrum disorder) and autism disorder are 3 to 4 times higher than 30 years ago.”**

Fombonne JAMA

Jan. 2003 / PMID 12503982

- Unless comparisons also control rigorously for changing case definitions, interpretation of differences in prevalence rates over time and across surveys will be virtually impossible.
- Moreover, there is strong evidence that differences in methods for case finding can account for a huge proportion of the variability of prevalence estimates between surveys.
- **Claims about an epidemic of autism and its putative causes have the most weak empirical support.**

Epigenetic

De novo

**Monogenic or
oligogenic
MEGDI model**

Inherited

Genetic

**MEGDI = mixed epigenetic & genetic and
de novo & inherited**