

How may Environmental Factors Impact Potential Molecular and Epigenetic Mechanisms?

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THE ETIOLOGY OF AUTISM

Autism

Genetic
40-50%?

Unknown
50-60%

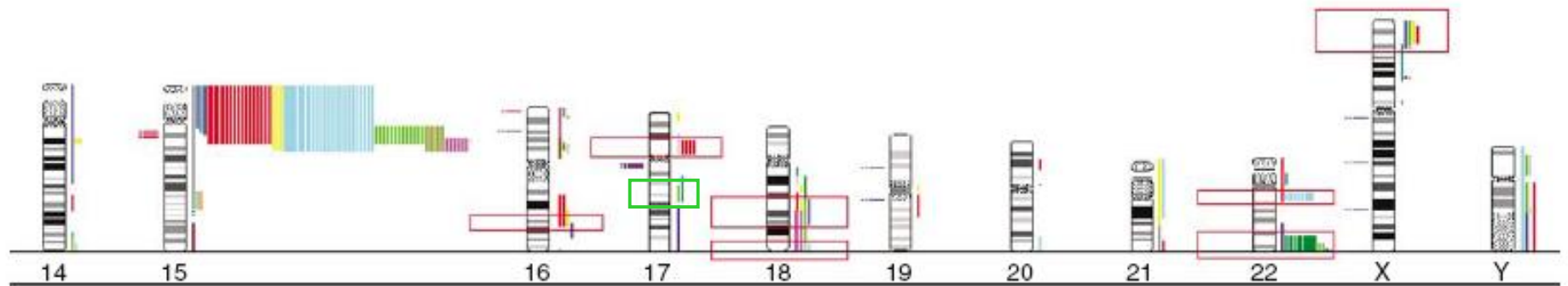
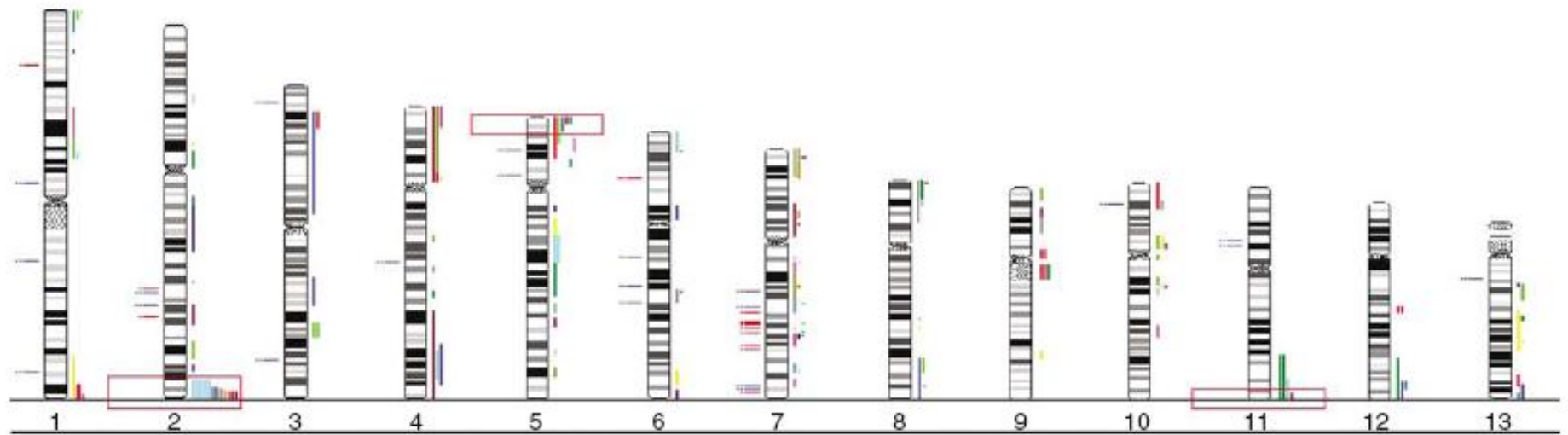
Chromosomal

Single gene

Dup 15q11-q13
Sex aneuploidy
De novo del / dup

Fragile X
Rett / *MECP2*
TSC1, TSC2, PTEN
NLGN4X, SHANK3

Genetic?
Epigenetic?
Environment?
Mixed?



Jacquemont et al. Array-based comparative genomic hybridisation identifies high frequency of cryptic chromosomal rearrangements in patients with syndromic autism spectrum disorders. PMID: 16840569

8/29 (27.5%) syndromic autism

Sebat et al. Strong Association of De Novo Copy Number Mutations with Autism. PMID: 17363630

12/118 (10%) simplex cases

2/196 (1%) controls

IMPLICATIONS:

Many more copy number mutations

Many more single gene point mutations

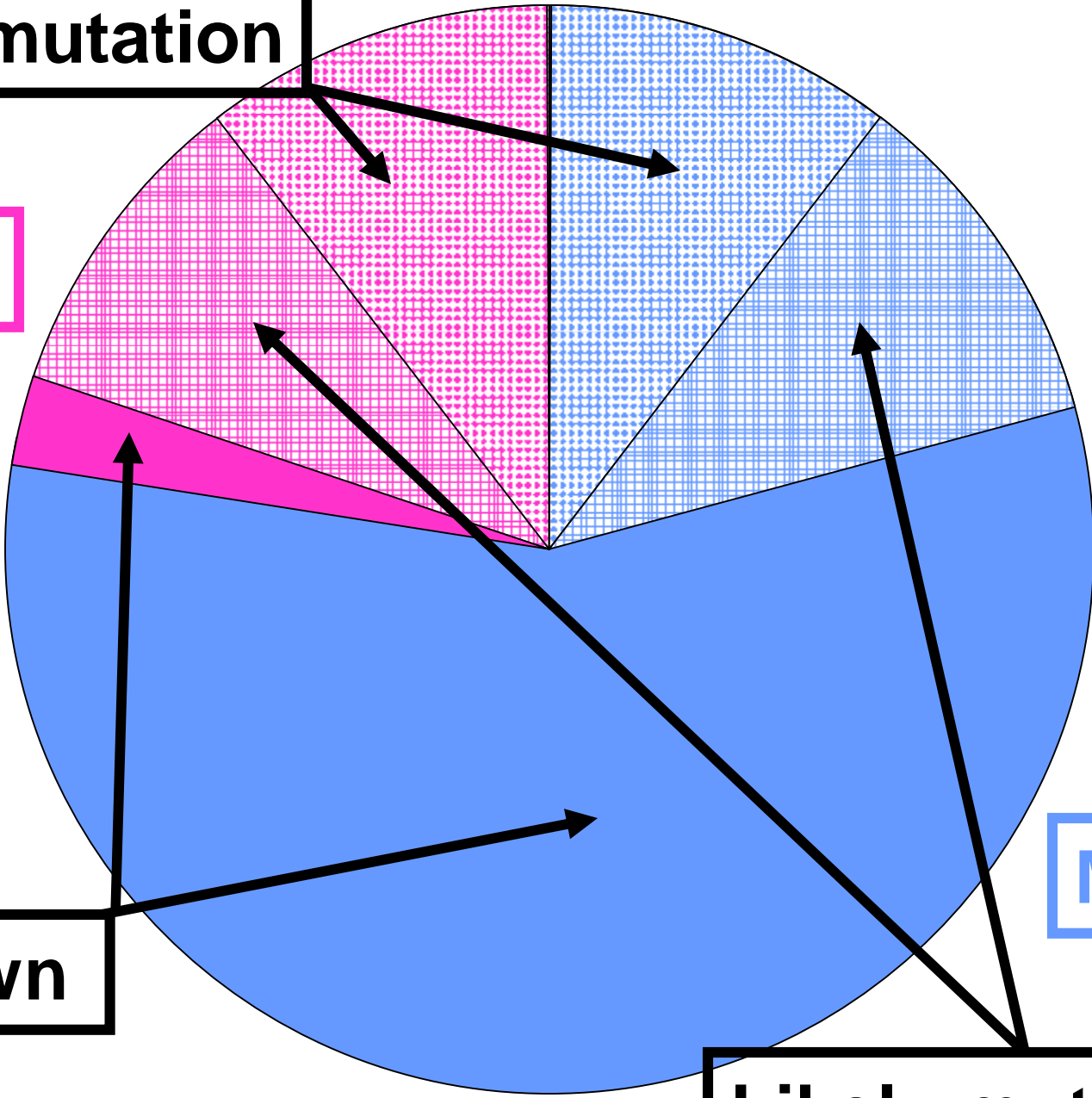
Advancing Paternal Age and Autism

*Abraham Reichenberg, PhD; Raz Gross, MD, MPH; Mark Weiser, MD;
Michealine Bresnahan, PhD; Jeremy Silverman, PhD; Susan Harlap, MBBS;
Jonathan Rabinowitz, PhD; Cory Shulman, PhD; Dolores Malaspina, MD;
Gad Lubin, MD; Haim Y. Knobler, MD;
Michael Davidson, MD; Ezra Susser, MD, DrPH*

Results: There was a significant monotonic association between advancing paternal age and risk of ASD. Offspring of men 40 years or older were 5.75 times (95% confidence interval, 2.65-12.46; *P*.001) more likely to have ASD compared with offspring of men younger than 30 years, after controlling for year of birth, socioeconomic status, and maternal age.

Known mutation

Female



Unknown

Male

Likely mutation

High MZ / low DZ twin concordance. Highly heritable but not inherited.

Disorder	MZ	DZ
Down syndrome	100%	<5%
Achondroplasia and Rett <i>de novo</i>	100%	nil
Autism imperical	60-90%	1-10%
Autism known genetic	100%	0-25%
De novo gametic or preMZ imprinting defect	100%	<5%

Prader-Willi

Angelman

Deletion

UPD

Deletion

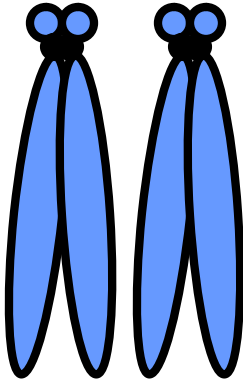
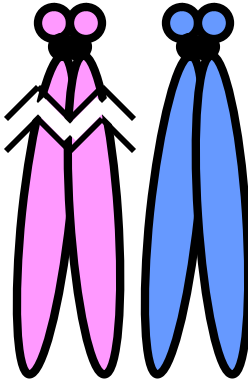
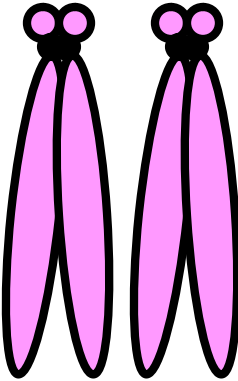
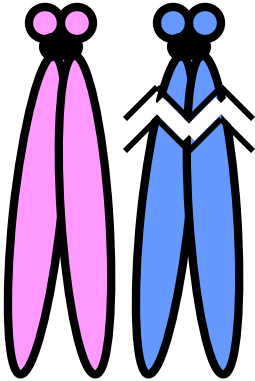
UPD

Genetic

Epigenetic

Genetic

Epigenetic



70%

30%

70%

rare

**Paternal deficiency
15q11-q13**

**Maternal deficiency
15q11-q13**

All deletions and UPD are *de novo* events

Epigenetic

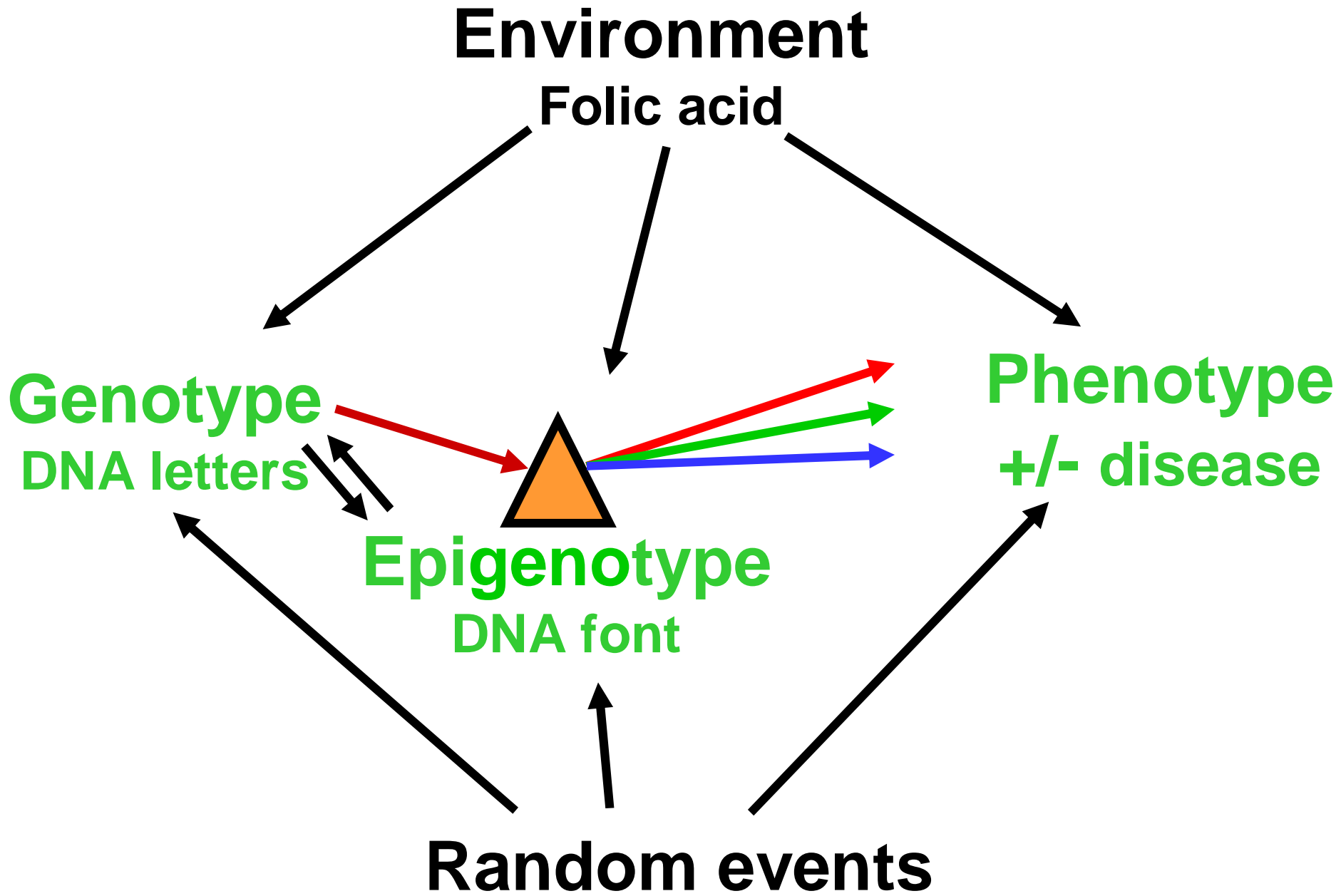
De novo

**Monogenic or
oligogenic
MEGDI model**

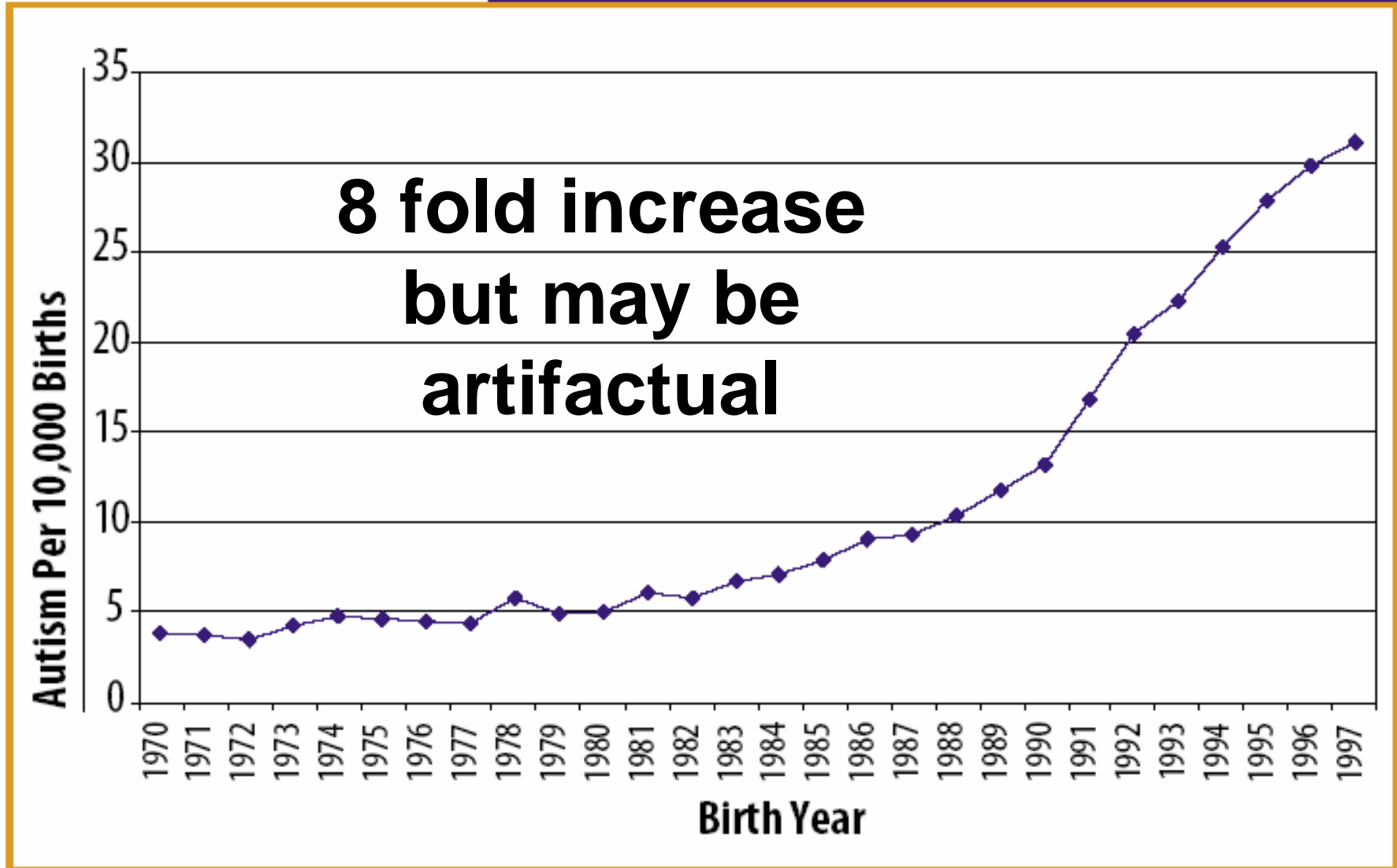
Inherited

Genetic

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



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



**IF THE INCIDENCE OF AUTISM
IS INCREASING, WHAT COULD
BE THE CAUSE?**

CANDIDATE FACTORS I

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

CANDIDATE FACTORS II

- **Tocolysis for preterm labor**
 - **Terbutaline toxicity in rats**
- **ART/ICSI & cryopreservation of embryos; ICSI and imprinting defects causing AS and BWS**
- **Chemical exposures**
- **Folate, vitamins, diet**

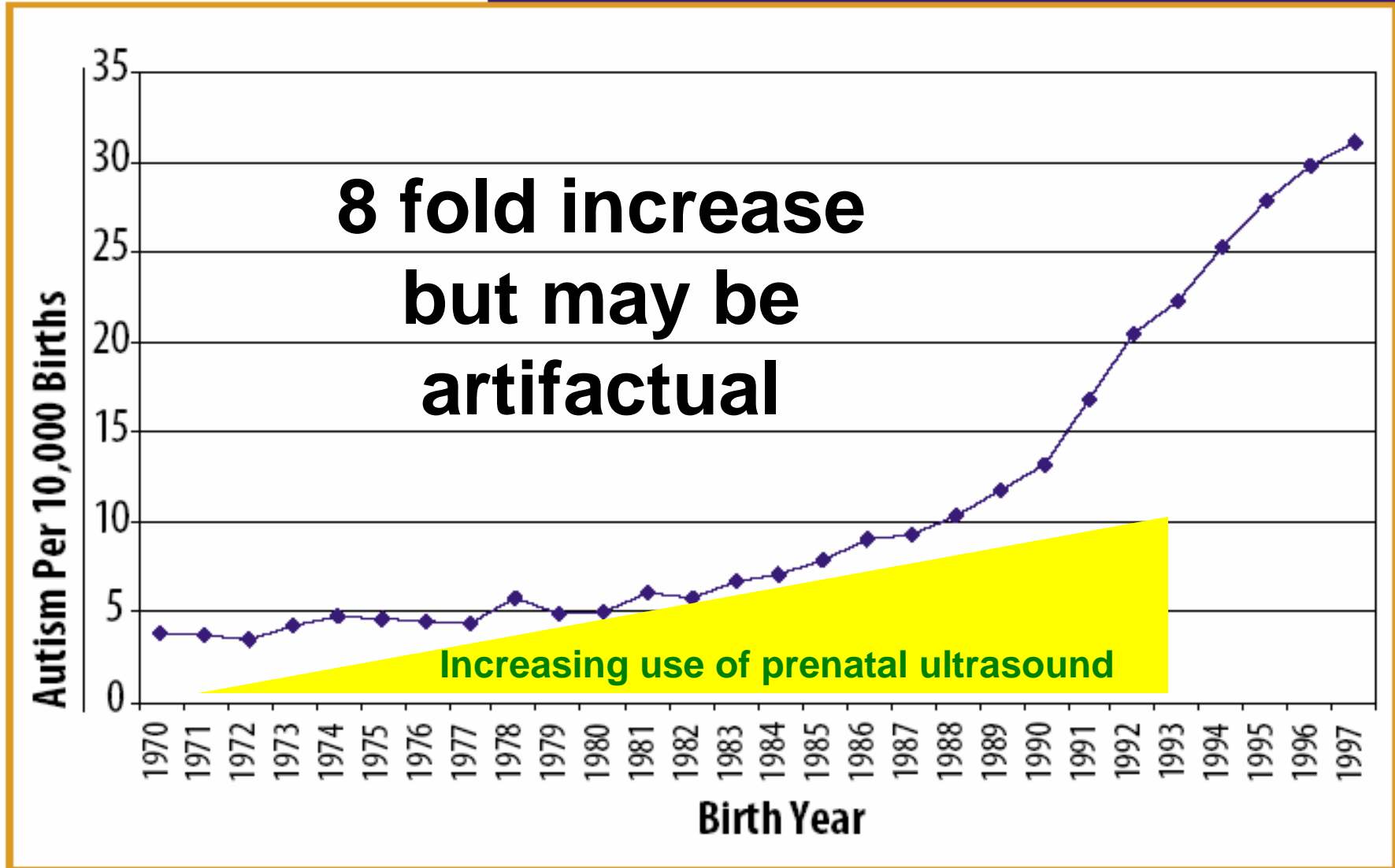
Prenatal exposure to ultrasound waves impacts neuronal migration in mice

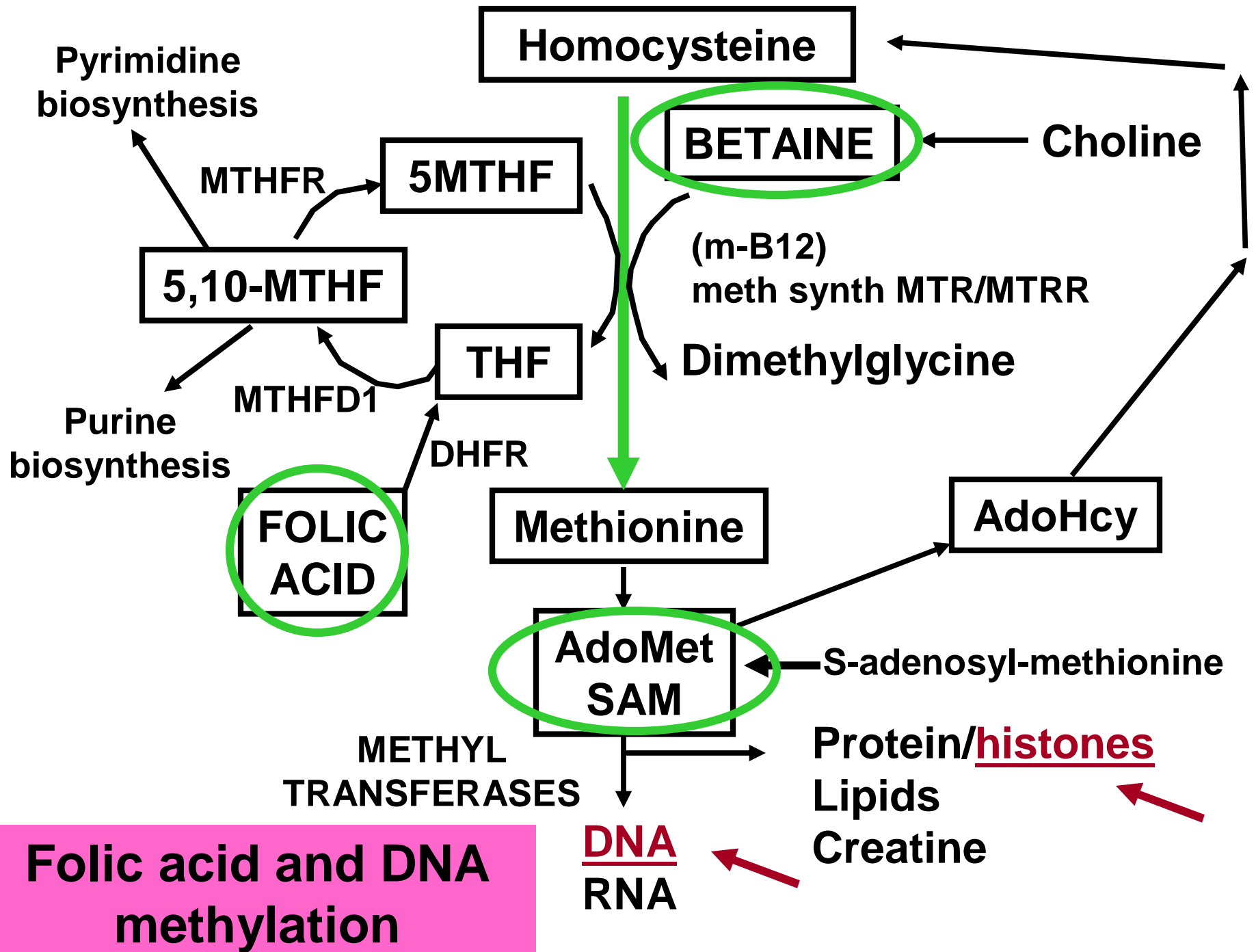
Eugenius S. B. C. Ang, Jr.*[†], Vicko Gluncic*[†], Alvaro Duque*, Mark E. Schafer[‡], and Pasko Rakic*[§]

*Department of Neurobiology and Kavli Institute for Neuroscience, Yale Medical School, Sterling Hall of Medicine, Room C-318, 333 Cedar Street, New Haven, CT 06510; and [‡]SonicTech, Inc., 23 Brookline Court, Ambler, PA 19002

Therefore, our results in pregnant mice support the recommendations by the Food and Drug Administration that **warn against the use of medically nonindicated or commercial prenatal ultrasound videos.** Our results also call for careful testing of the nonthermal effects of USW at the potentially vulnerable intense period of cortical neurogenesis in the human fetus. Furthermore, **it is essential to examine the possible effects of USW on cortical development in non-human primates,** where the duration of embryogenesis and the size and complexity of migratory pathways are more similar to those in humans.

**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

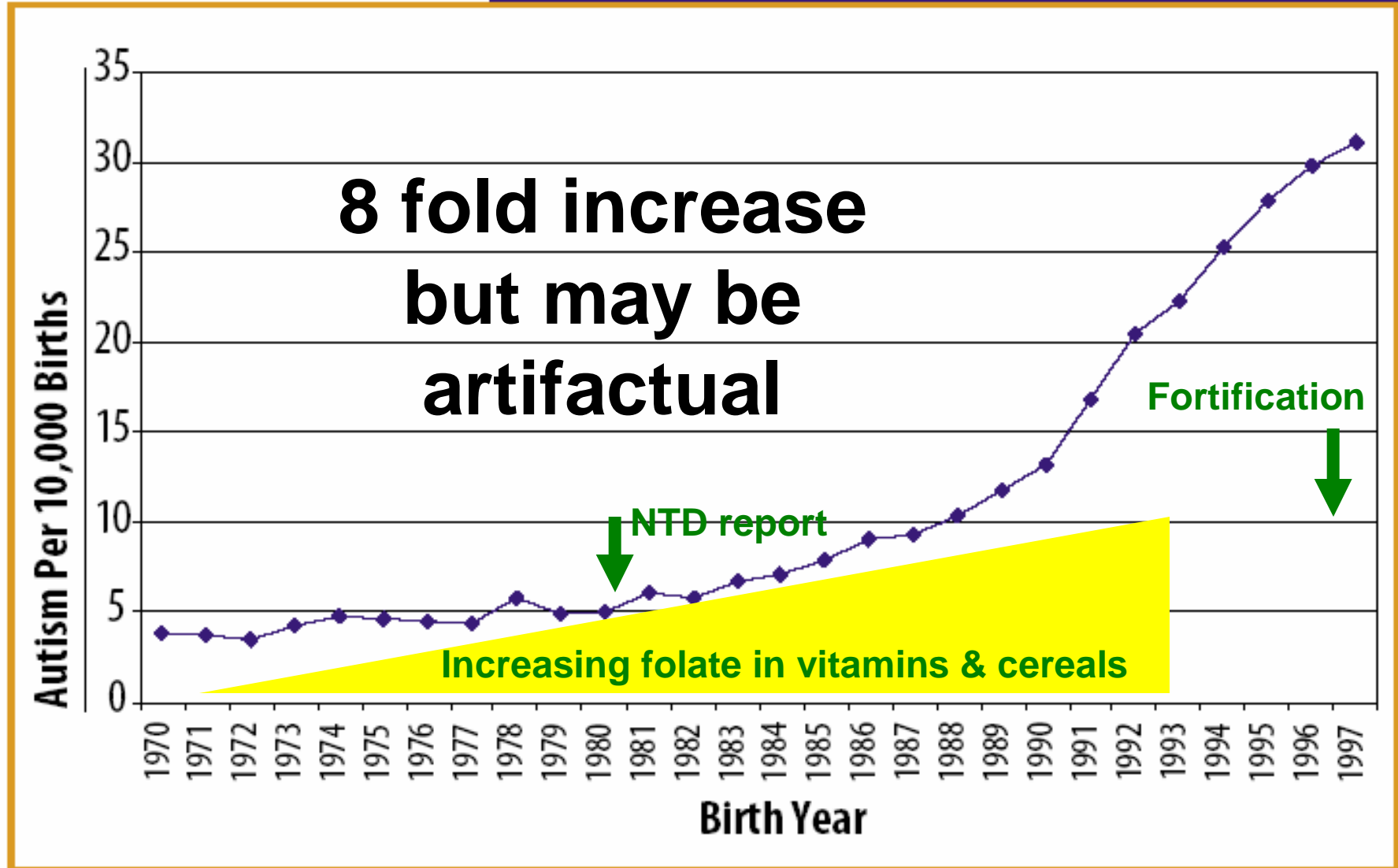
- NHANES I (1971-74) --- 23 %
- NHANES II (1976-80) --- 35 %
- NHANES III (1988-94) --- 42 %
- Through 1999 --- ~40 %
- **VITACREST**; 1972; 0.1 mg folic acid
- **1973**; OTC limit raised to 0.4 mg folic acid
- **ONE-A-DAY**; none to 1976; then 0.4 mg
- **VIDAYLIN**; none to 1977; then 0.4 mg

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

**Figure 3 - Uncorrected Birth Year
Prevalence Rates from 1970 through
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Low folic acid

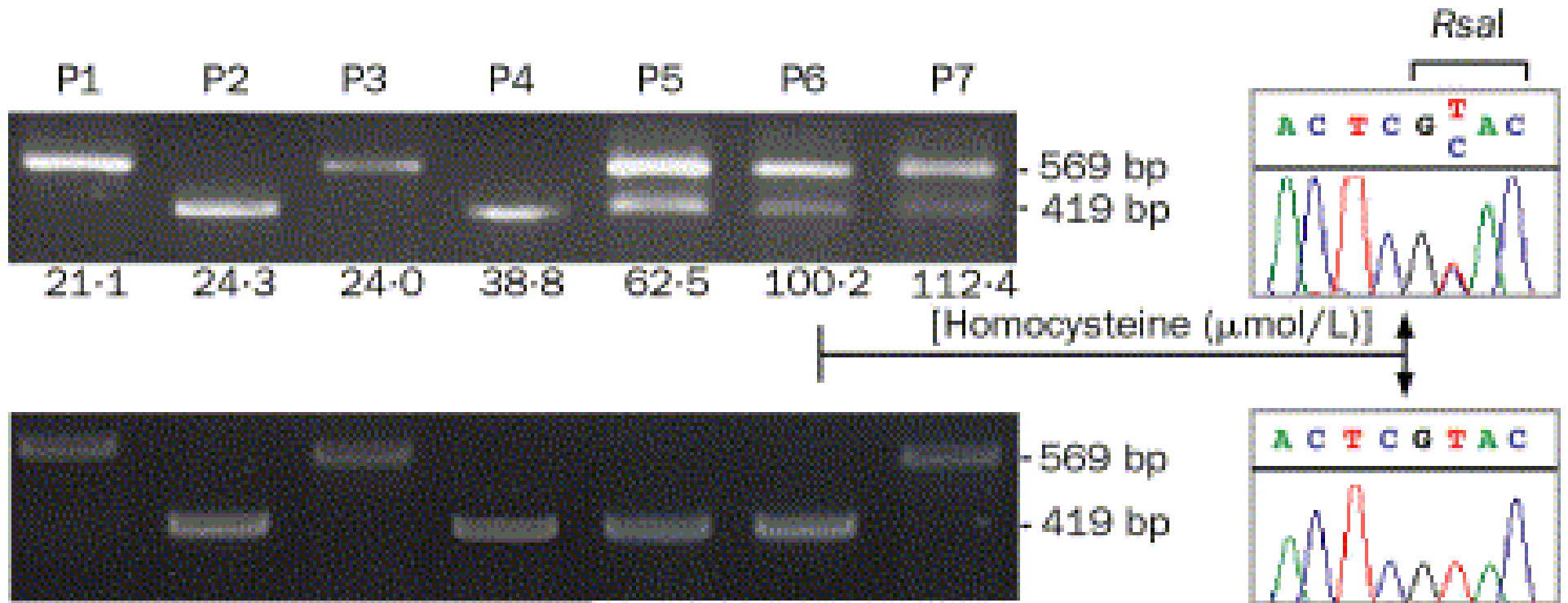
High folic acid

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**

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

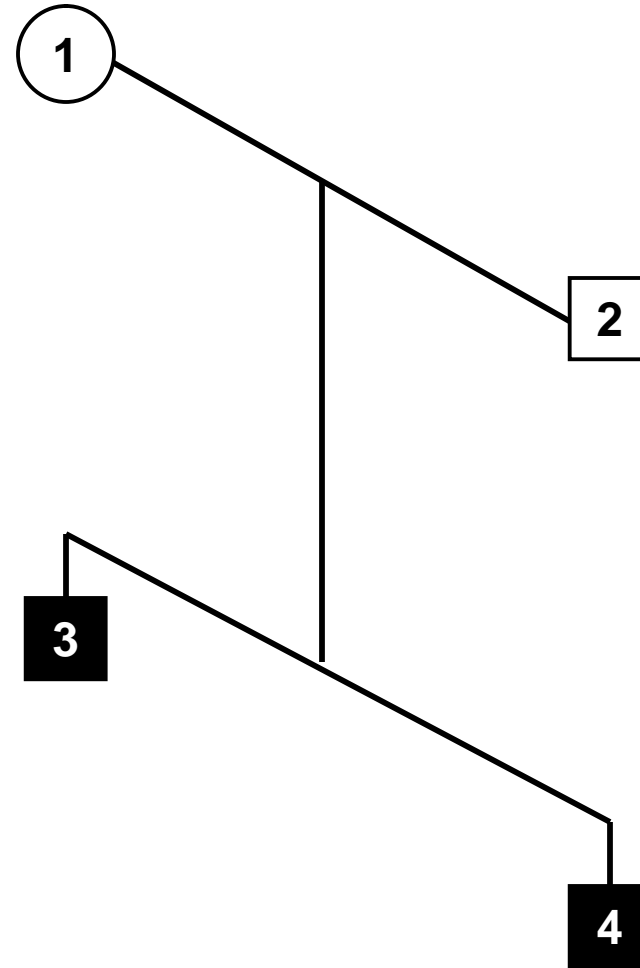
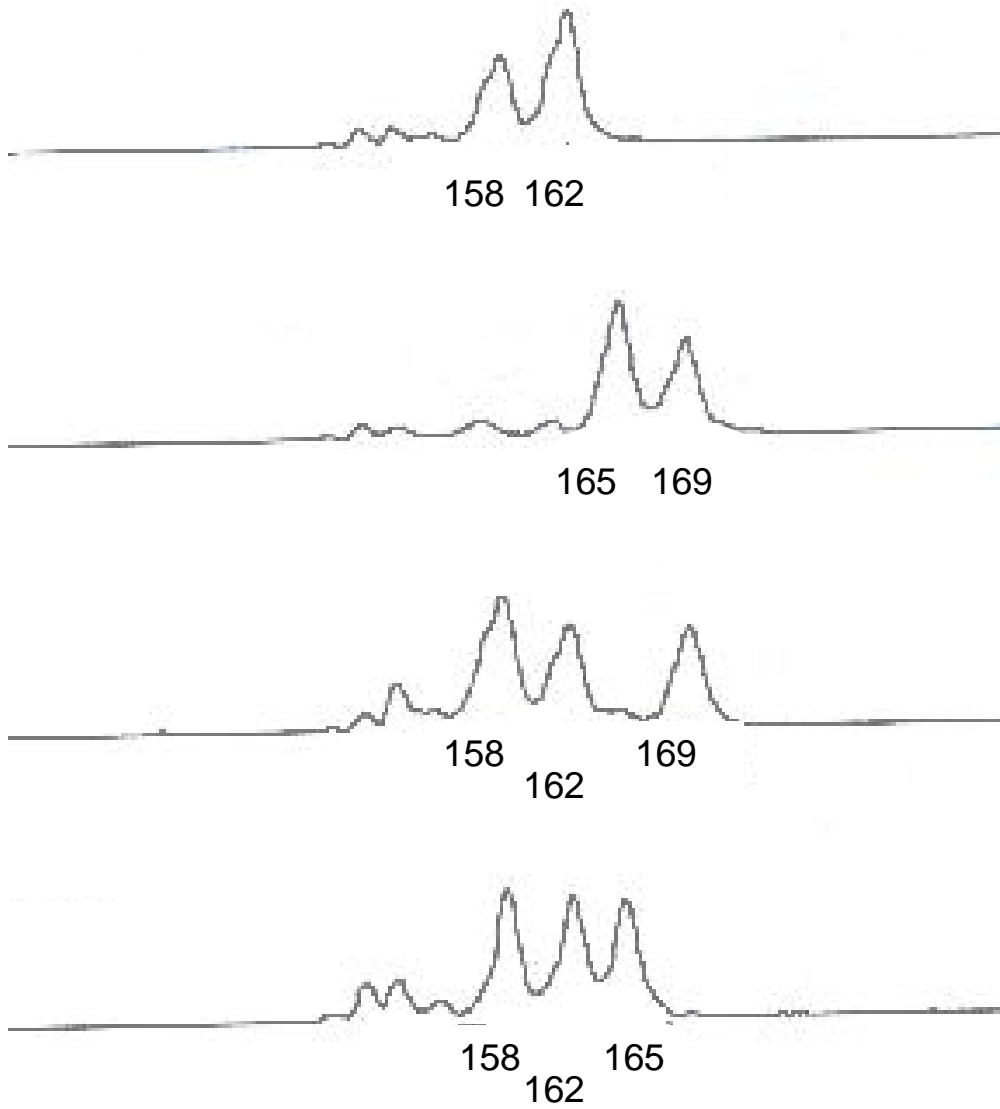
**We need to know more about
whether folic acid intake is
increasing or decreasing the
incidence of any diseases!**

SUGGESTIONS

- **Genome-wide studies at the exon and single base level**
- **Separate the strong mutation group out**
- **Epigenetic approaches to the idiopathic group**

END

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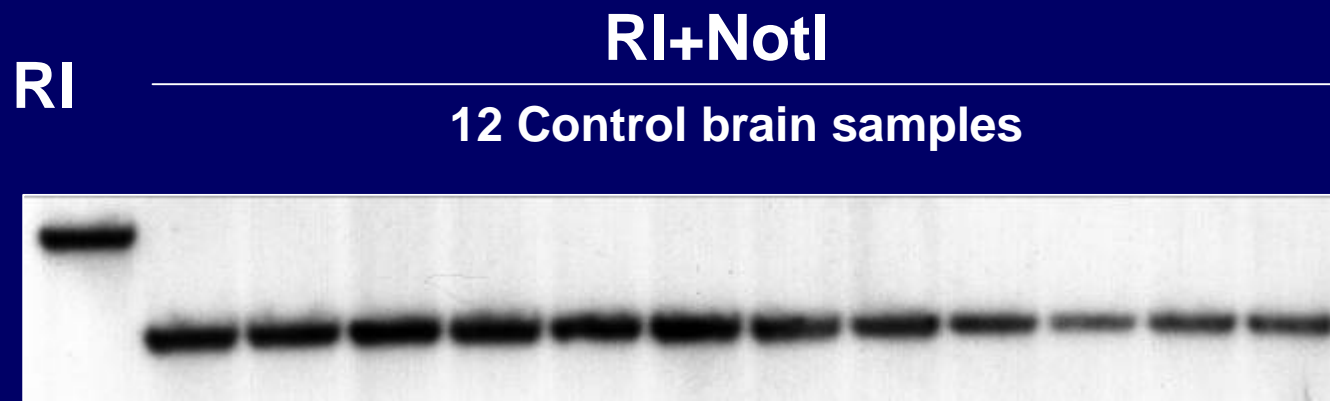


D15S817

SHORT TANDEM REPEAT

T Sahoo

CHANGE IN ANGELMAN GENE IN 1/17 AUTISM BRAINS



AU-1a AU-1b AU-3 AU5 NL



NotI+EcoRI

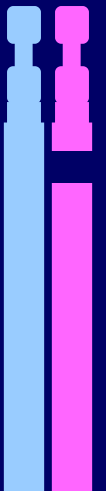

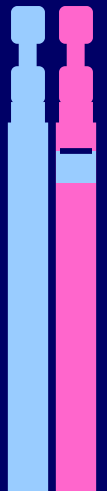

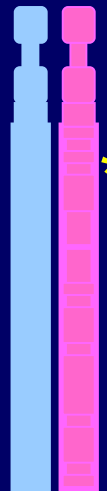
Yong-hui Jiang

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?

Angelman

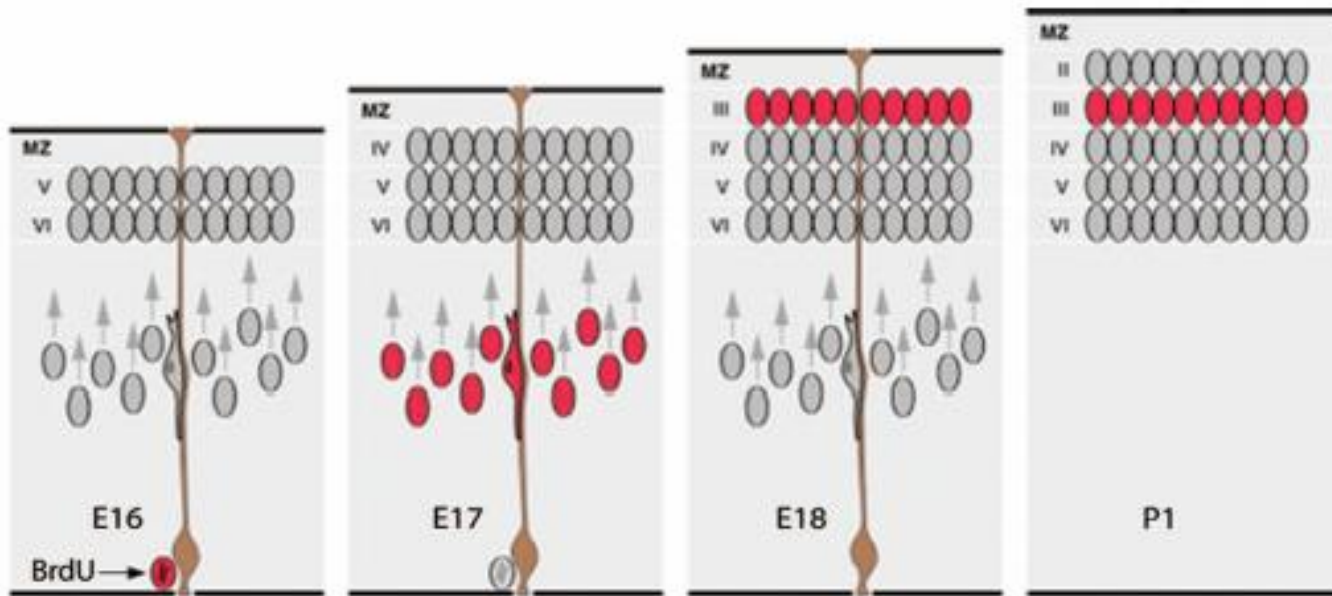
de novo	de novo	de novo & inherited	de novo	de novo & inherited
Deletion	UPD	Imprint Defect IC del	Imprint Defect no IC del	<i>UBE3A</i> Null
Genetic	Epi-genetic	Mixed	Epi-genetic	Genetic
				
			ICSI?	

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

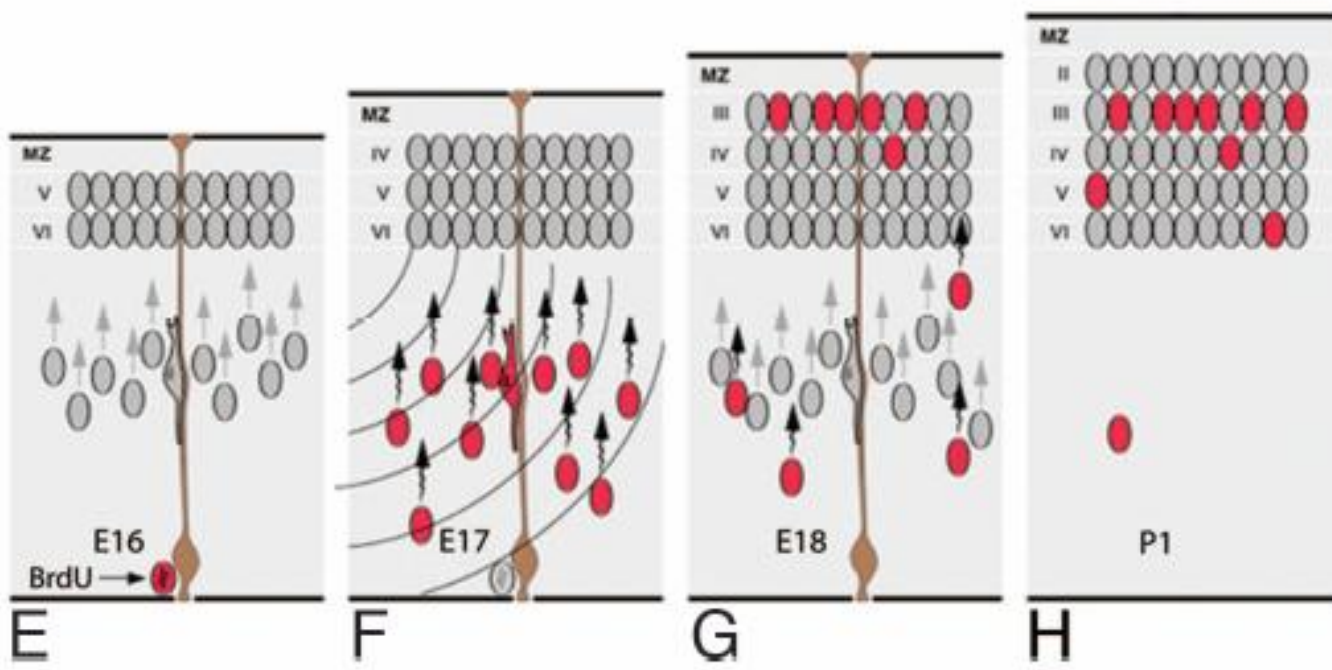
Heterogeneity of types of defects causing one phenotype

PWS, BWS, & GNAS disorders similar

Our analysis of over 335 animals reveals that, when exposed to USW for a total of 30 min or longer during the period of their migration, a small but statistically significant number of neurons fail to acquire their proper position and remain scattered within inappropriate cortical layers and or in the subjacent white matter.



**A-D
Normal**



**E-H
USW**