How may Environmental Factors Impact Potential Molecular and Epigenetic Mechanisms?

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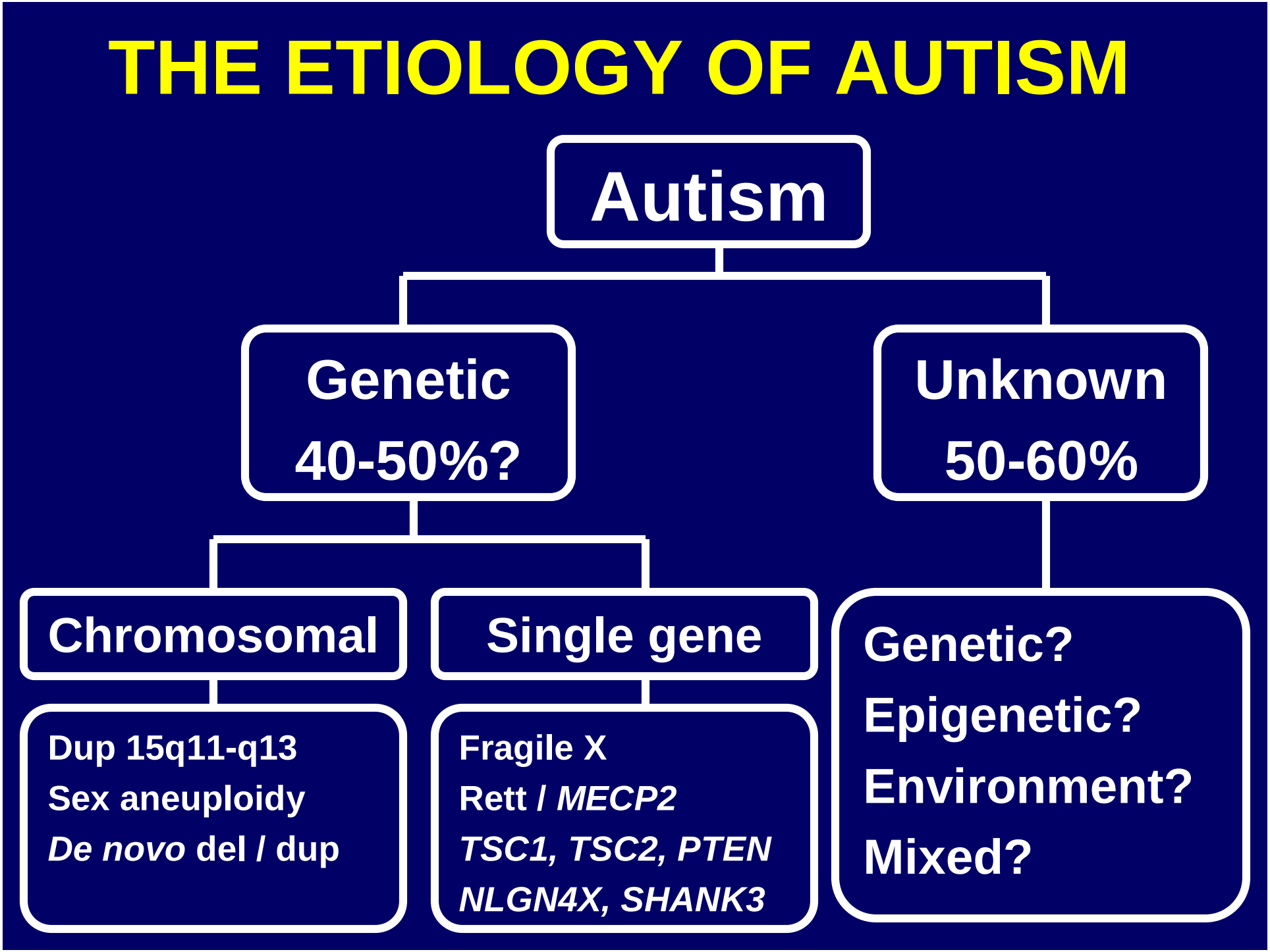
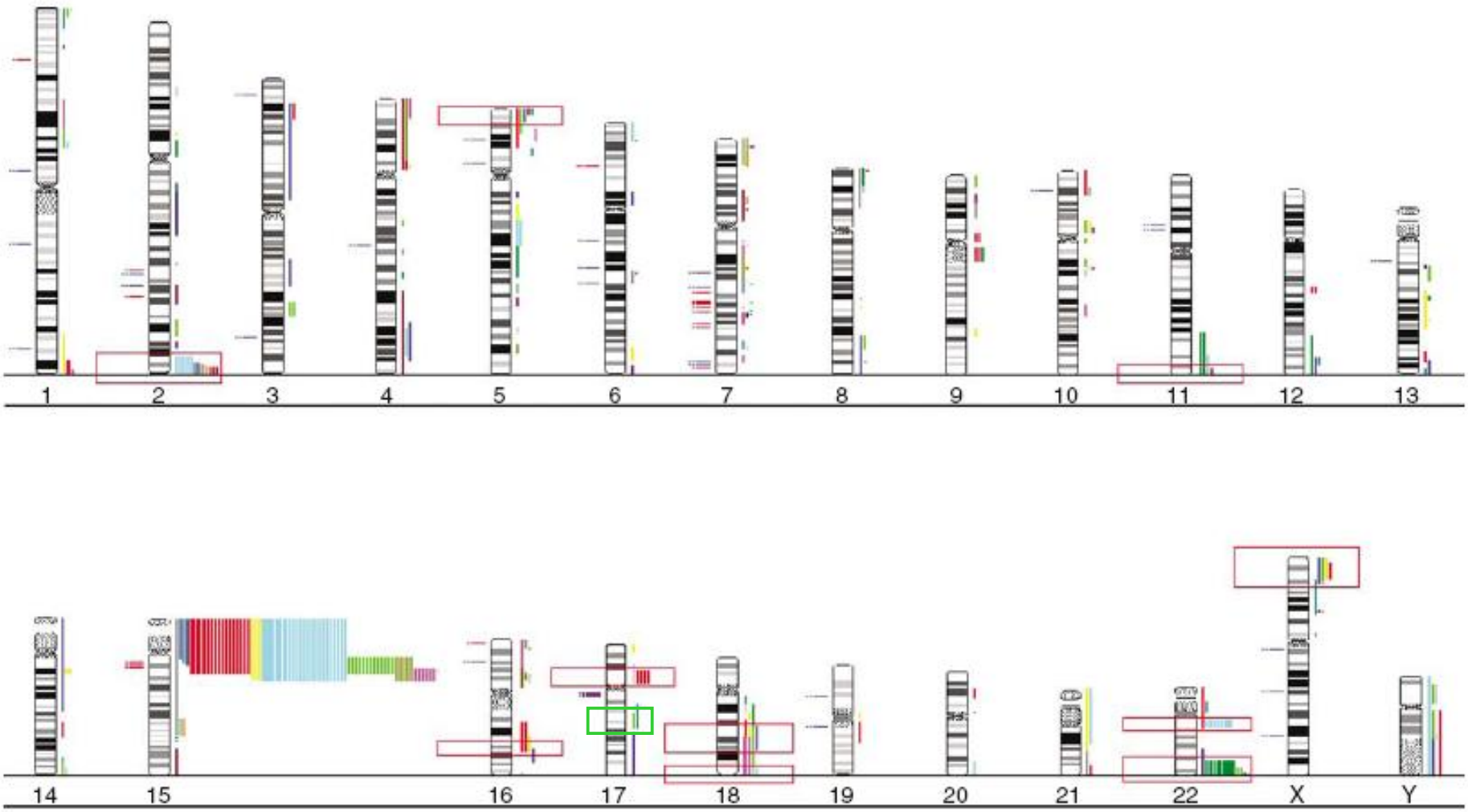
THE ETIOLOGY OF AUTISM

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22
X
Y

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:

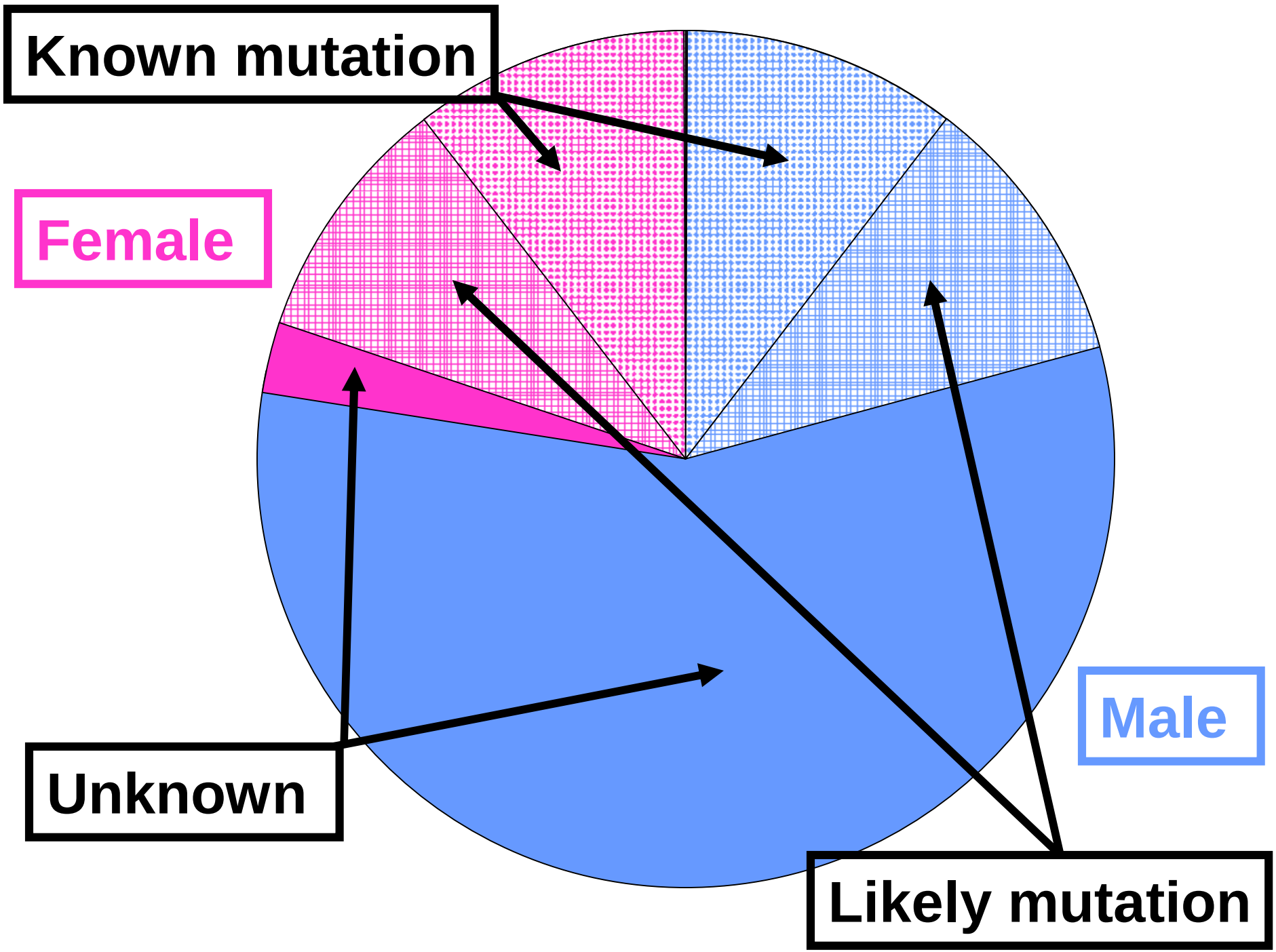
Many more copy number mutations

Many more single gene point mutations

Advancing Paternal Age and Autism

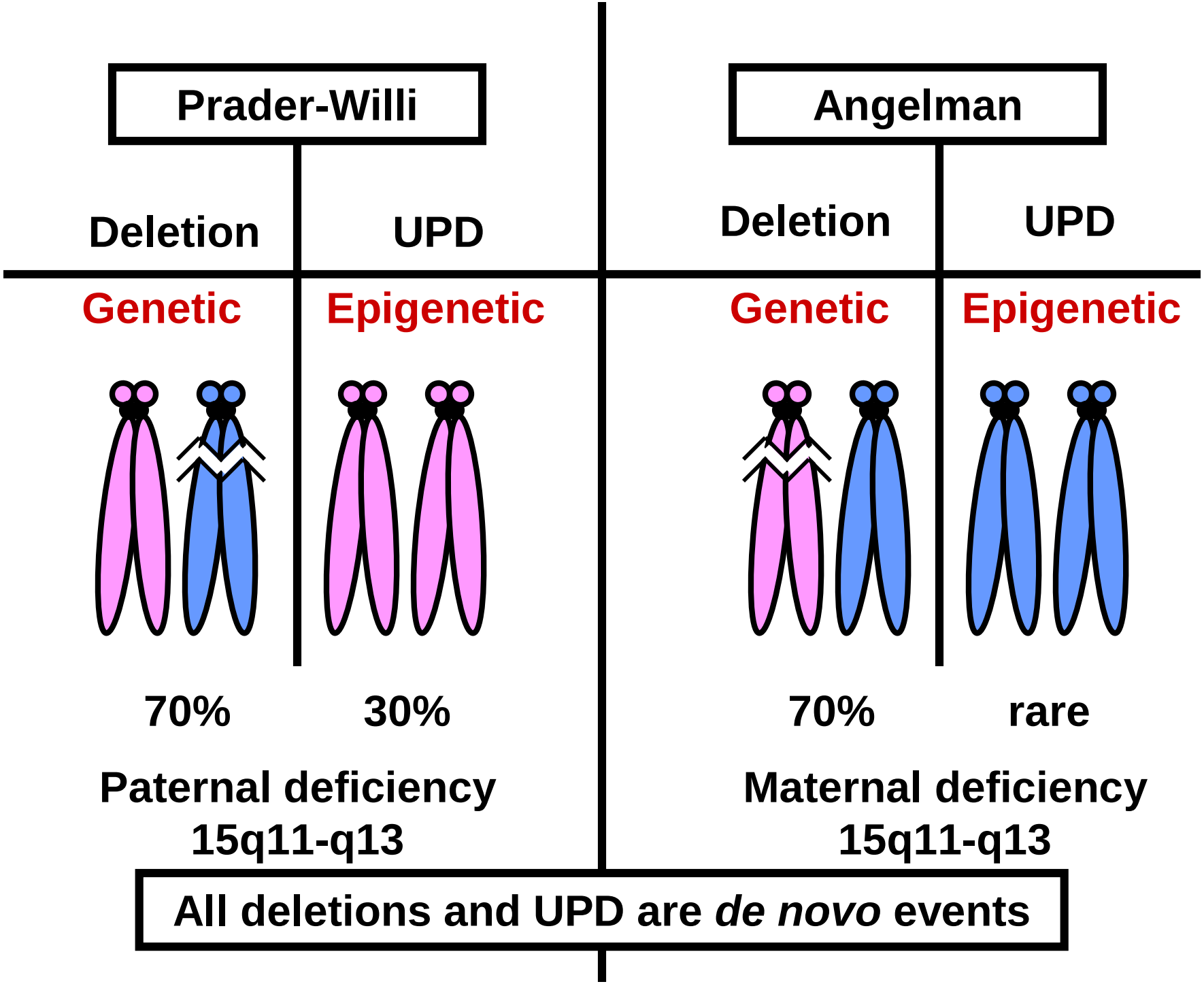
Abraham Reichenberg, PhD; Raz Gross, MD, MPH; Mark Weiser, MD; Michealine Bresnahan, PhD; Jeremy Silverman, PhD; Susan Harlap, MBBS; Jonathan Rabinowitz, PhD; Cory Shulman, PhD; Dolores Malaspina, MD; Gad Lubin, MD; Haim Y. Knobler, MD; Michael Davidson, MD; Ezra Susser, MD, DrPH

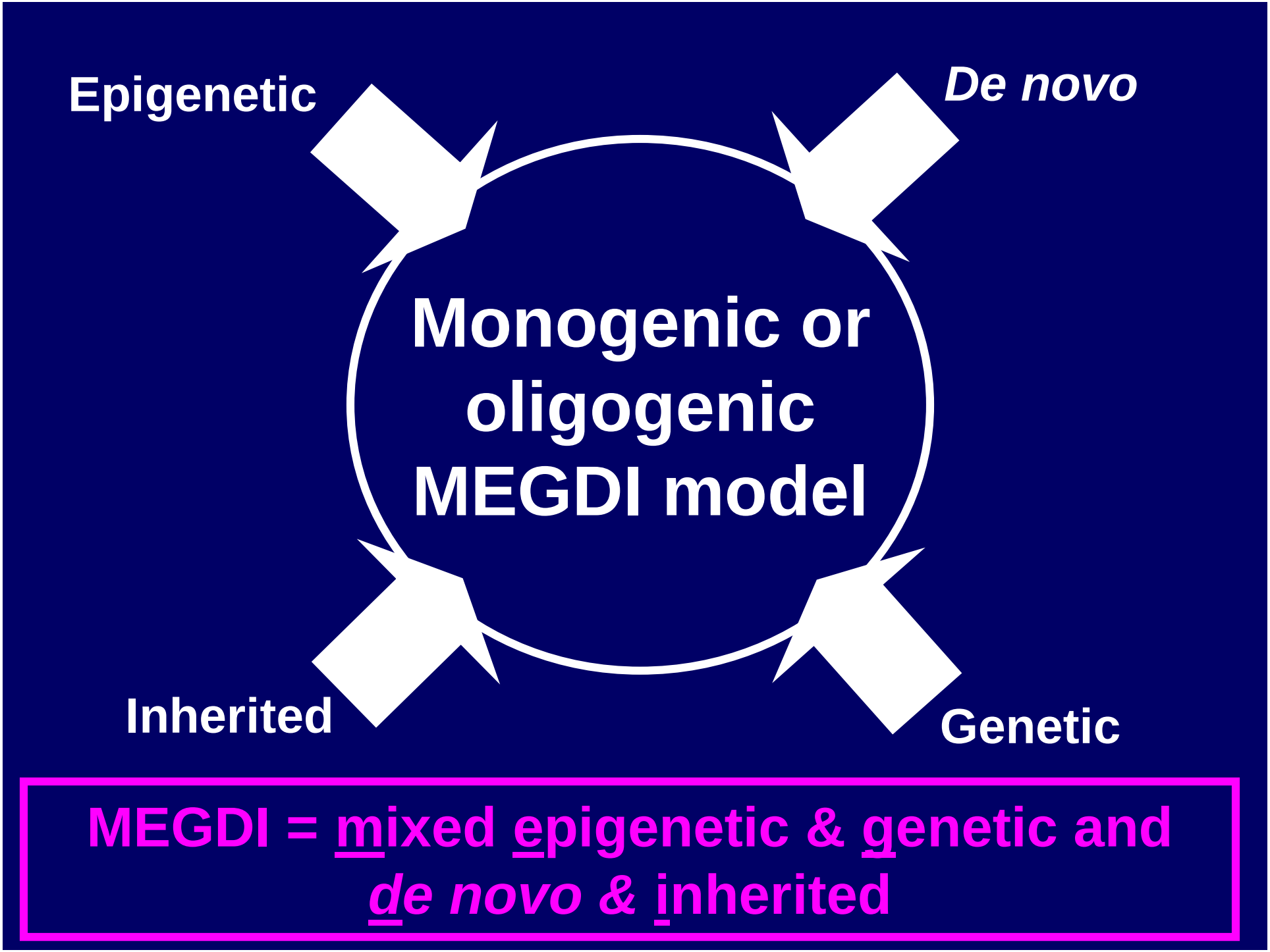
Results: There was a significant monotonic association between advancing paternal age and risk of ASD. Offspring of men 40 years or older were 5.75 times (95% confidence interval, 2.65-12.46; *P*.001) more likely to have ASD compared with offspring of men younger than 30 years, after controlling for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

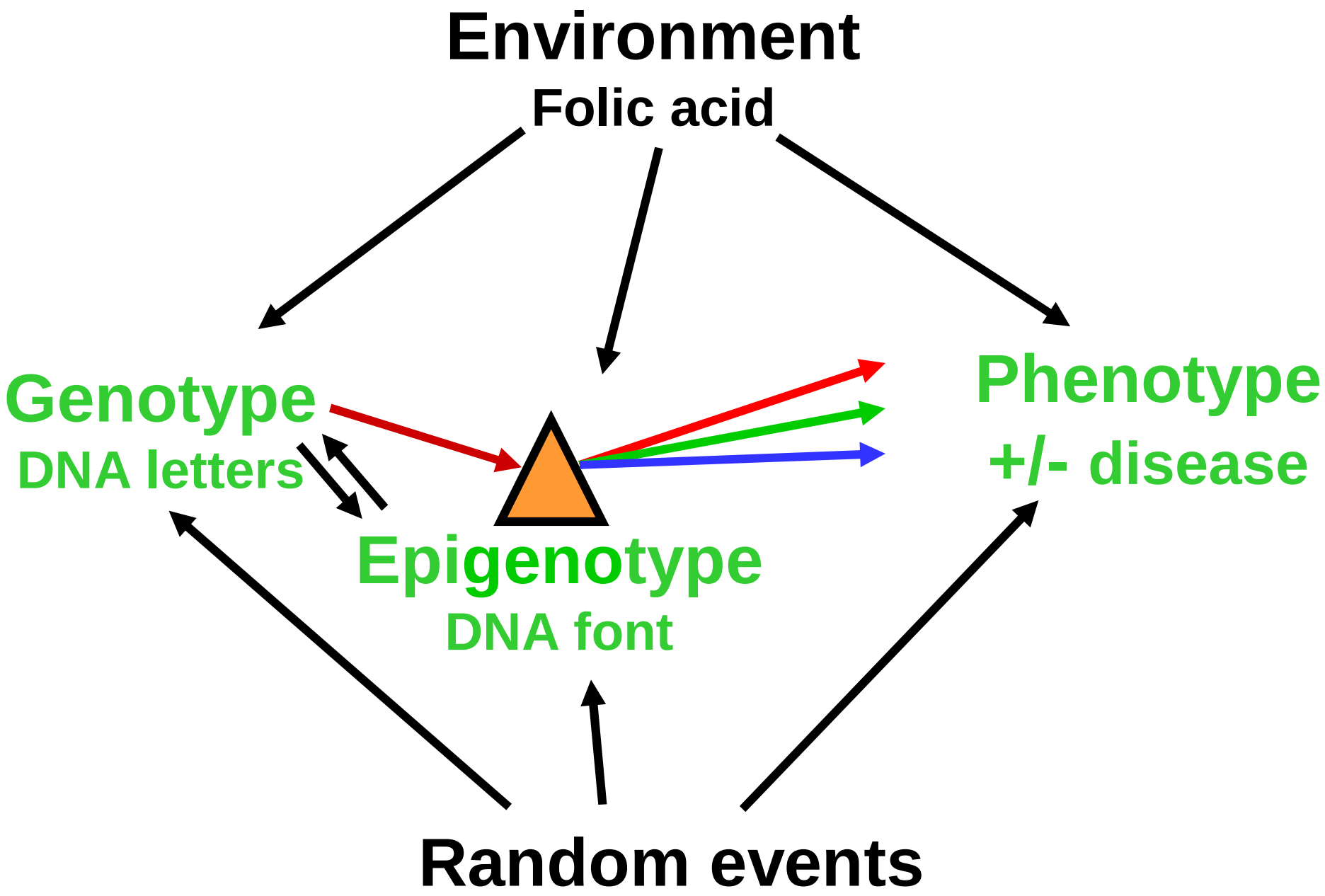

Known mutation
Female
Male
Unknown
Likely mutation

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

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

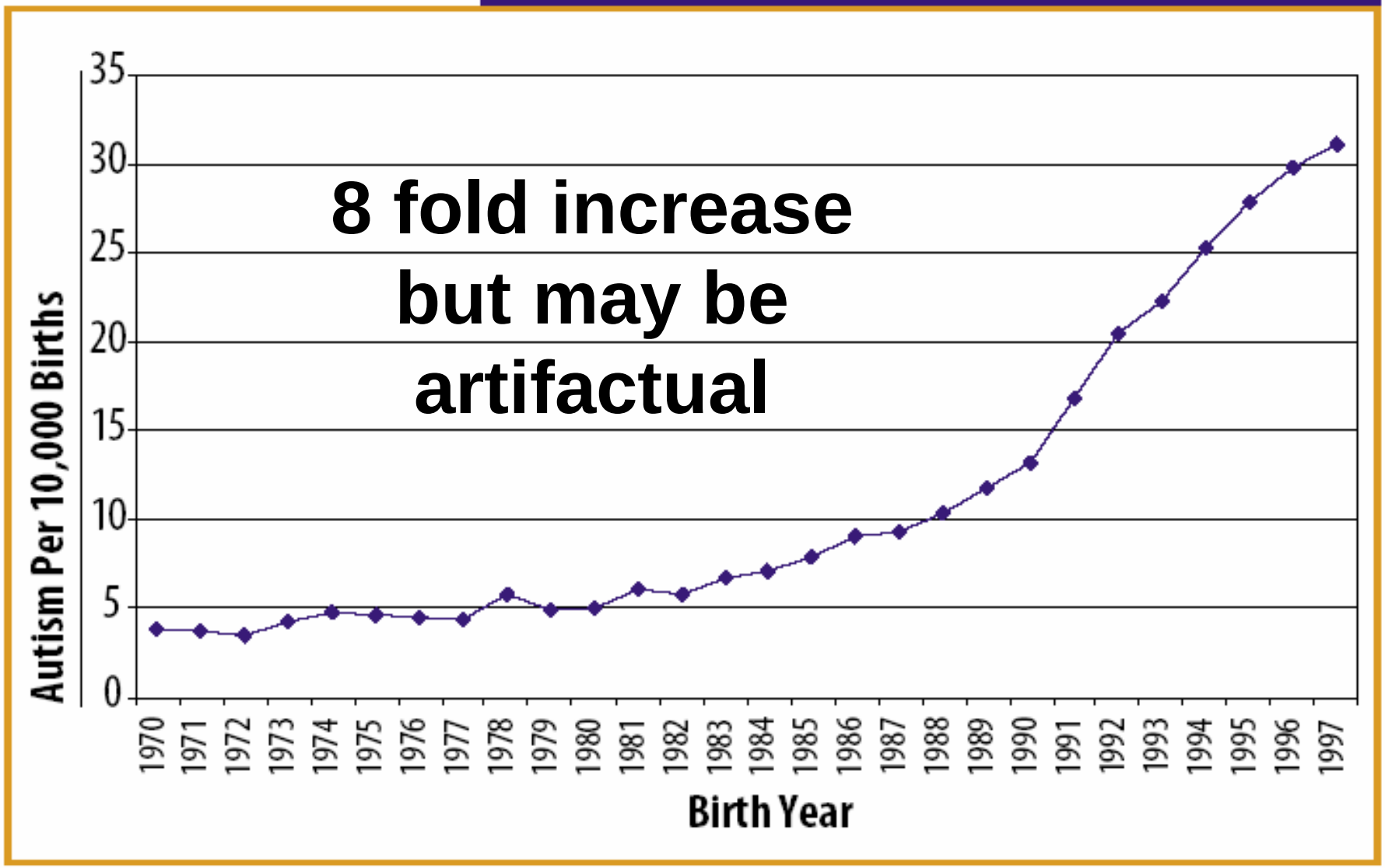

Prader-Willi
Angelman
Deletion
UPD
Deletion
UPD
Genetic
Epigenetic
Genetic
Epigenetic
70%
30%
70%
rare
Paternal deficiency
15q11-q13
Maternal deficiency
15q11-q13
All deletions and UPD are *de novo* events


Epigenetic
De novo
Monogenic or oligogenic MEGDI model
Inherited
Genetic
MEGDI = mixed epigenetic & genetic and de novo & inherited


Environment
Folic acid
Genotype
DNA letters
Epigenotype
DNA font
Phenotype
+/- disease
Random events

California Department of Developmental Services
www.dds.ca.gov

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.

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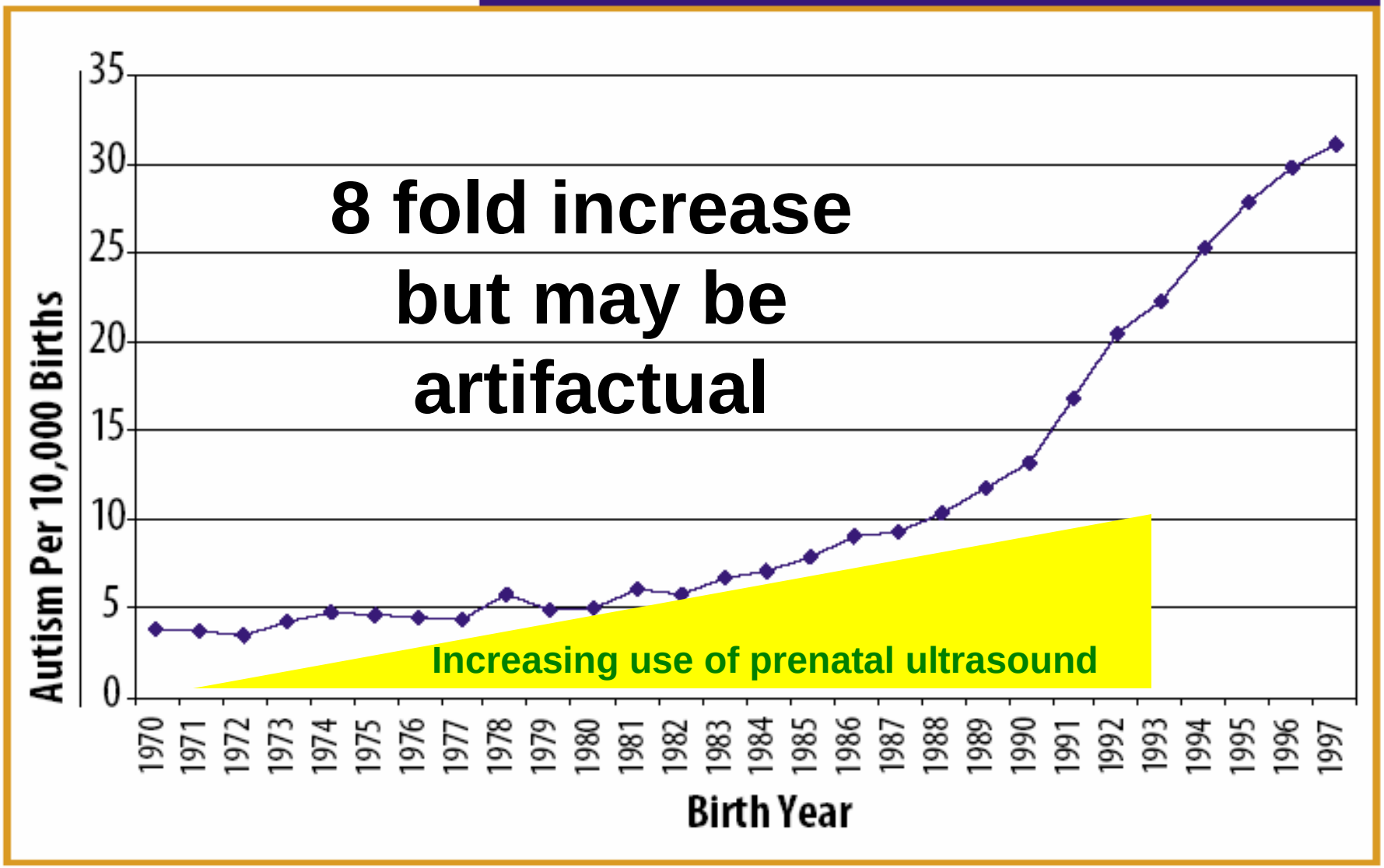

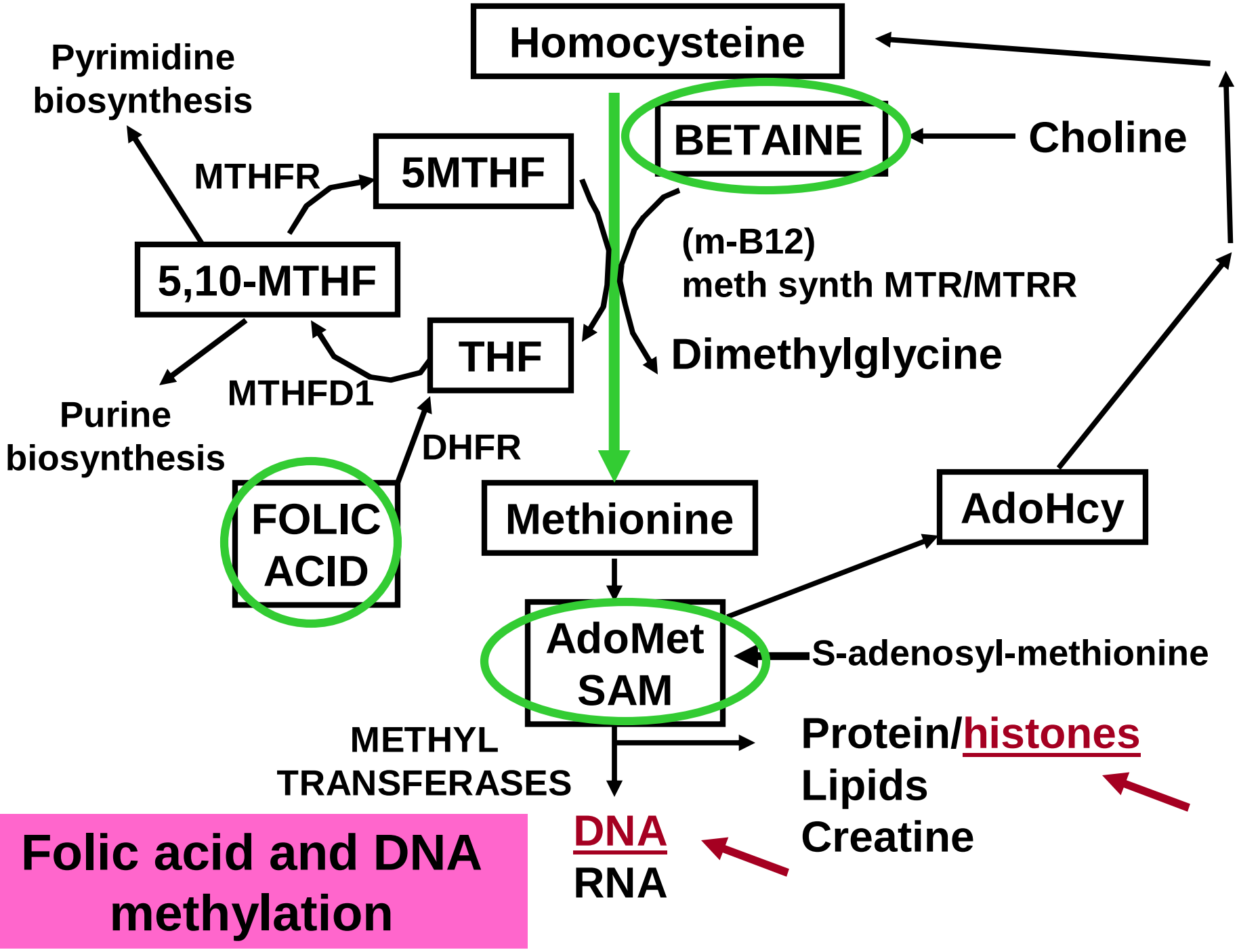
Homocysteine
Pyrimidine biosynthesis
BETAINE
Choline
MTHFR
5MTHF
(m-B12)
meth synth MTR/MTRR
5,10-MTHF
Dimethylglycine
THF
MTHFD1
Purine biosynthesis
DHFR
FOLIC ACID
Methionine
AdoHcy
AdoMet SAM
S-adenosyl-methionine
METHYL TRANSFERASES
Protein/histones
Lipids
Creatine
DNA
RNA
Folic acid and DNA methylation

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

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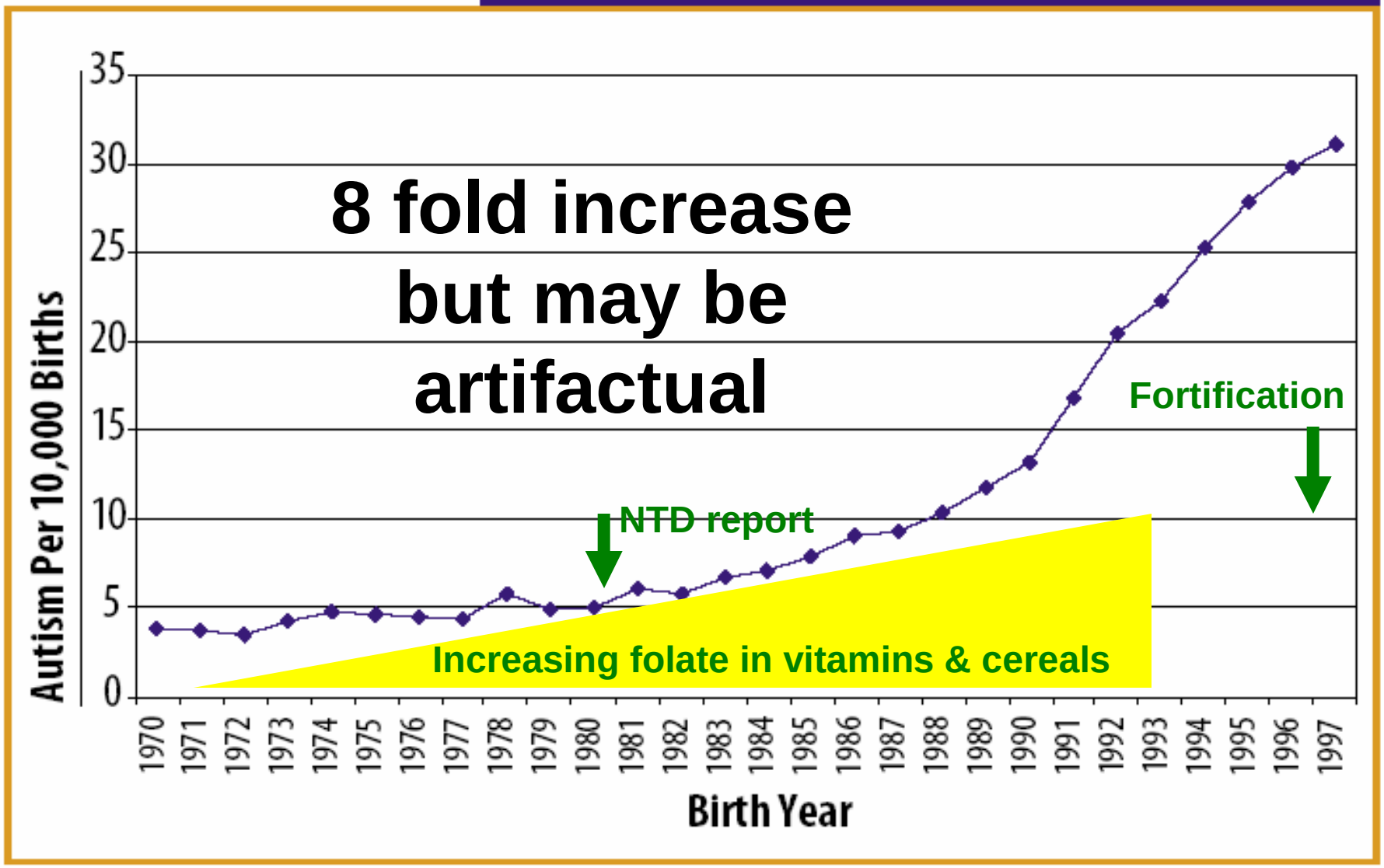


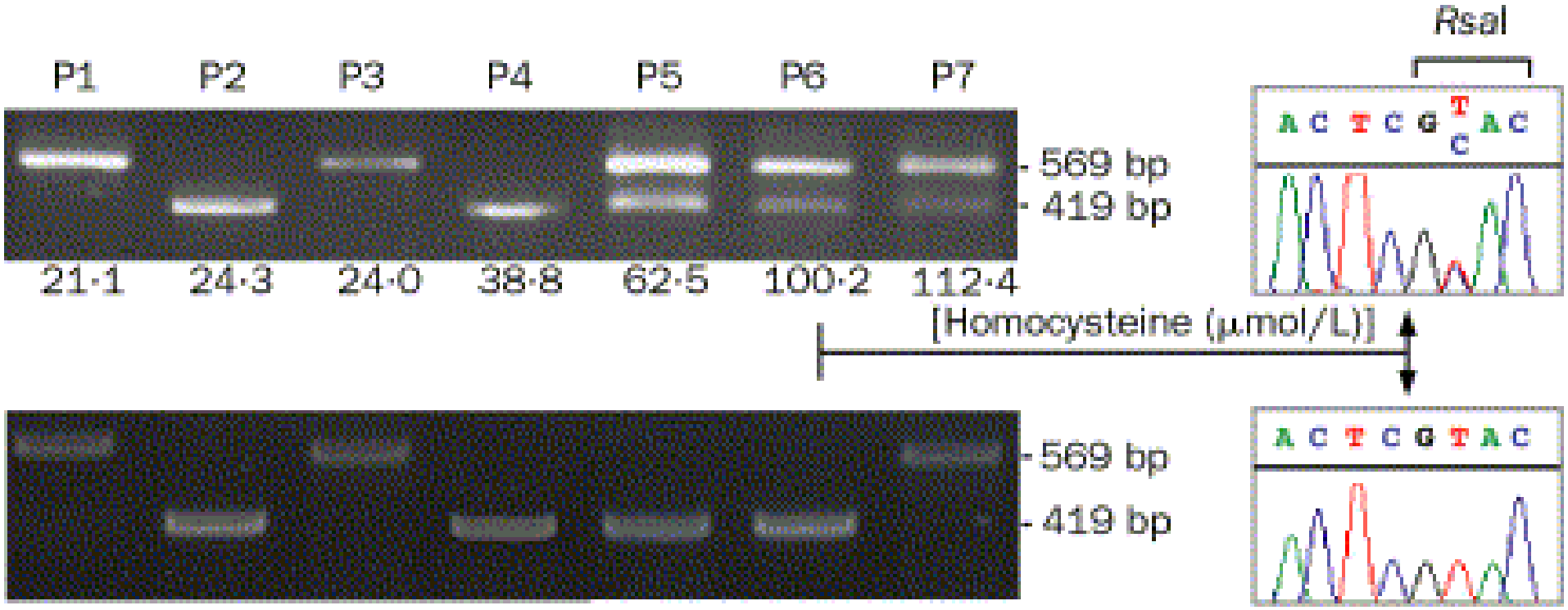
Low folic acid

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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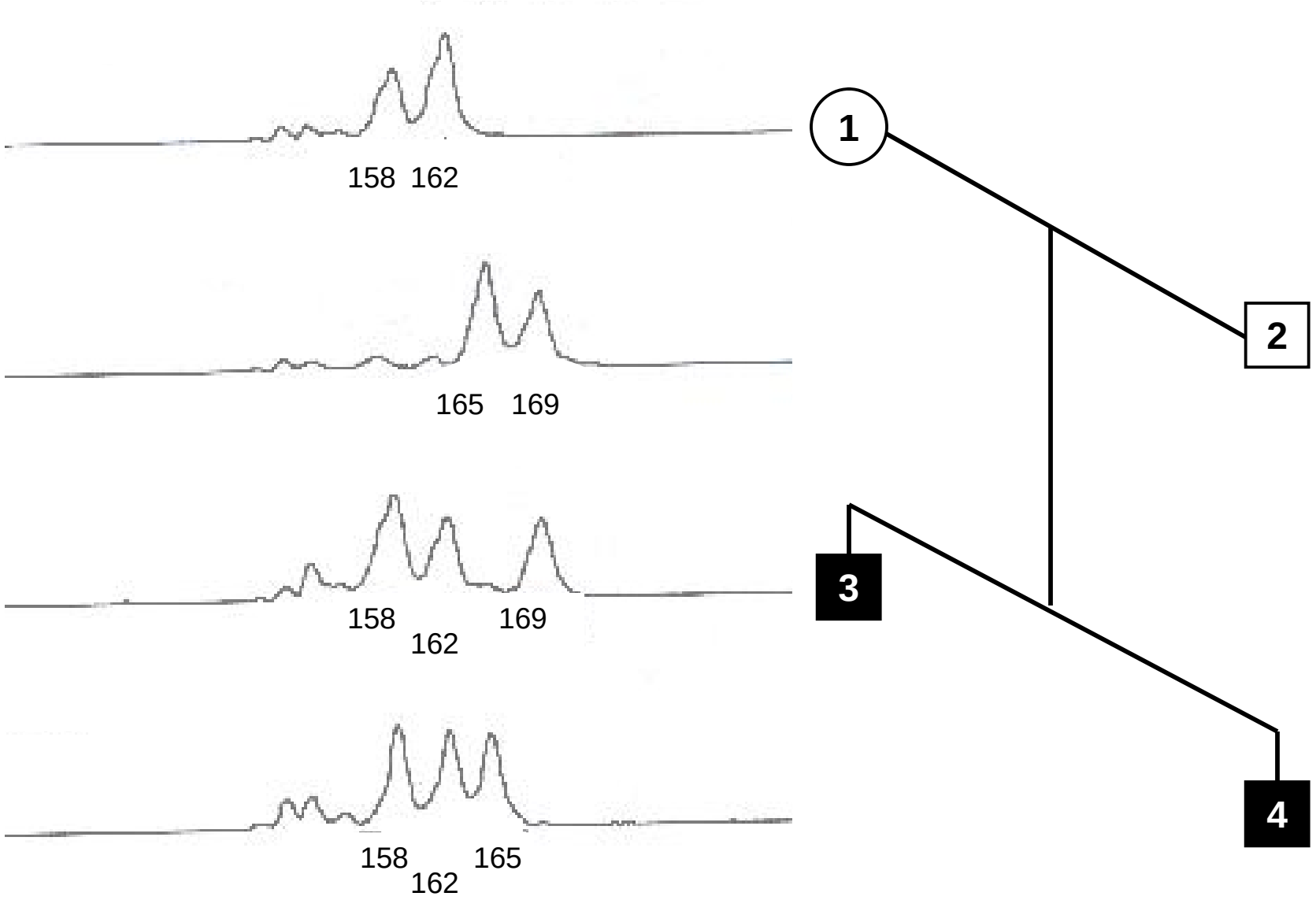
Baylor College of Medicine



D15S817

SHORT TANDEM REPEAT

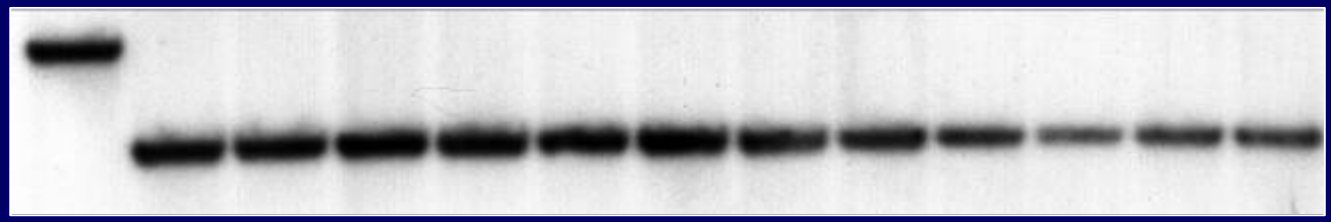
T Sahoo

CHANGE IN ANGELMAN GENE IN 1/17 AUTISM BRAINS

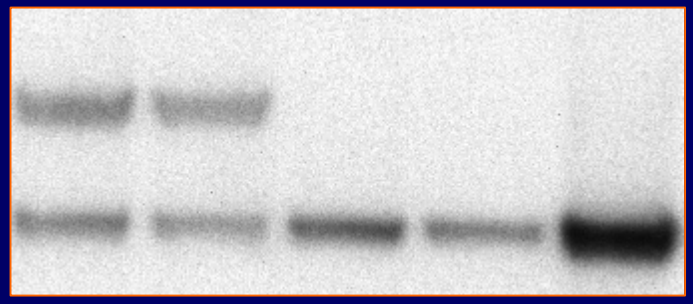
RI

RI+NotI

12 Control brain samples

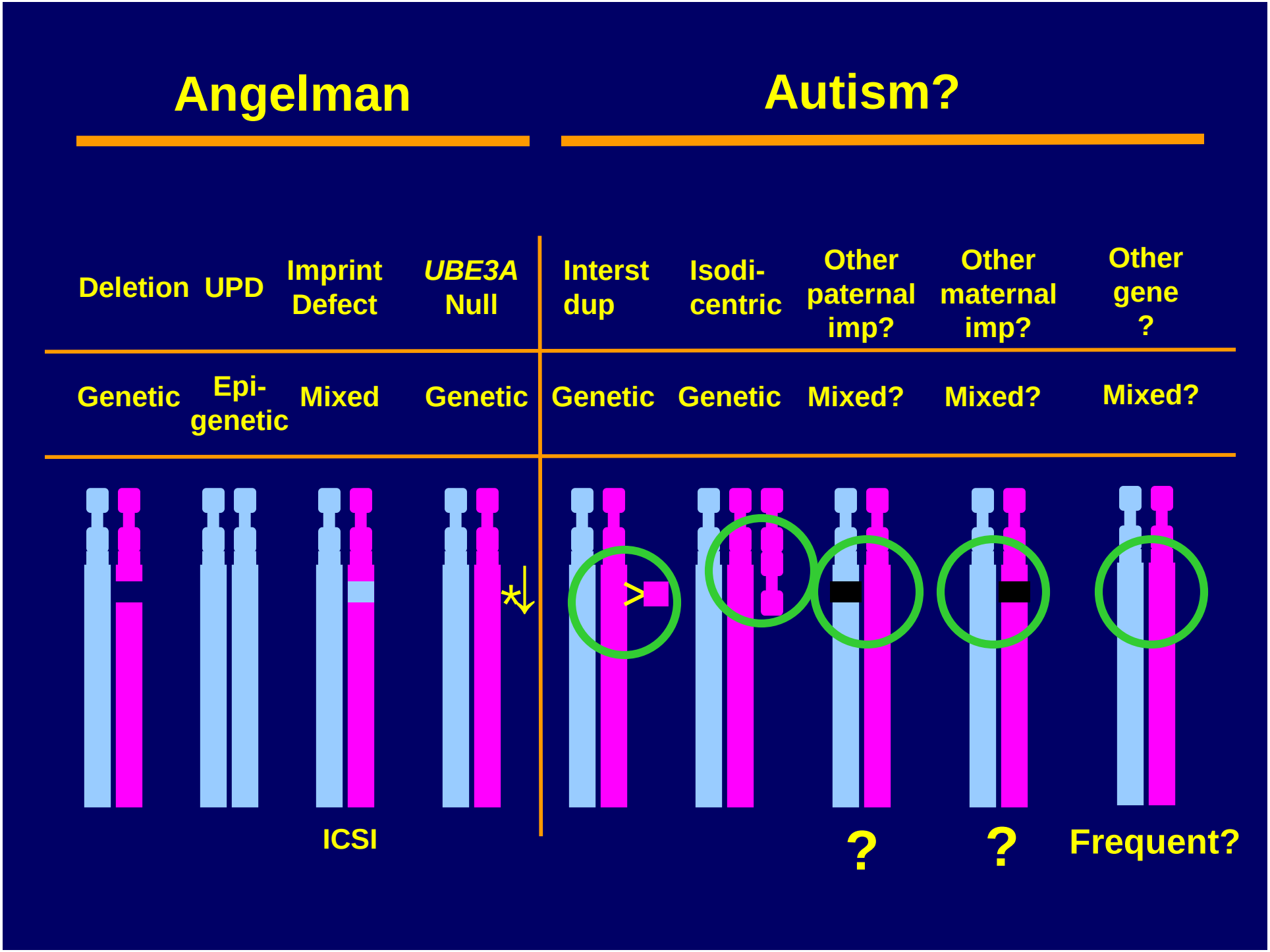


AU-1a AU-1b AU-3 AU5 NL



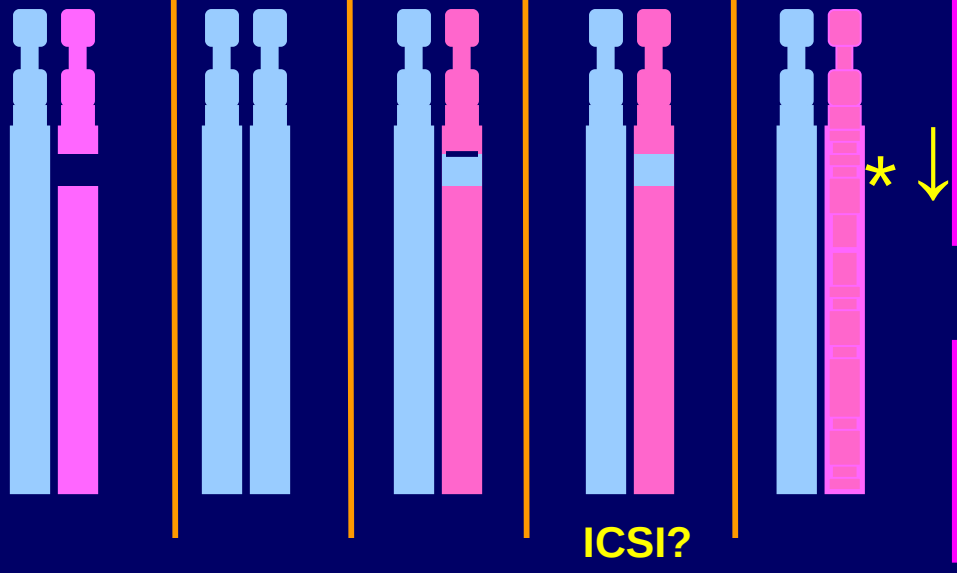
NotI+EcoRI

Yong-hui Jiang


Angelman
Autism?
Deletion
UPD
Imprint Defect
UBE3A 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	*UBE3A* Null
Genetic	Epi-genetic	Mixed	Epi-genetic	Genetic

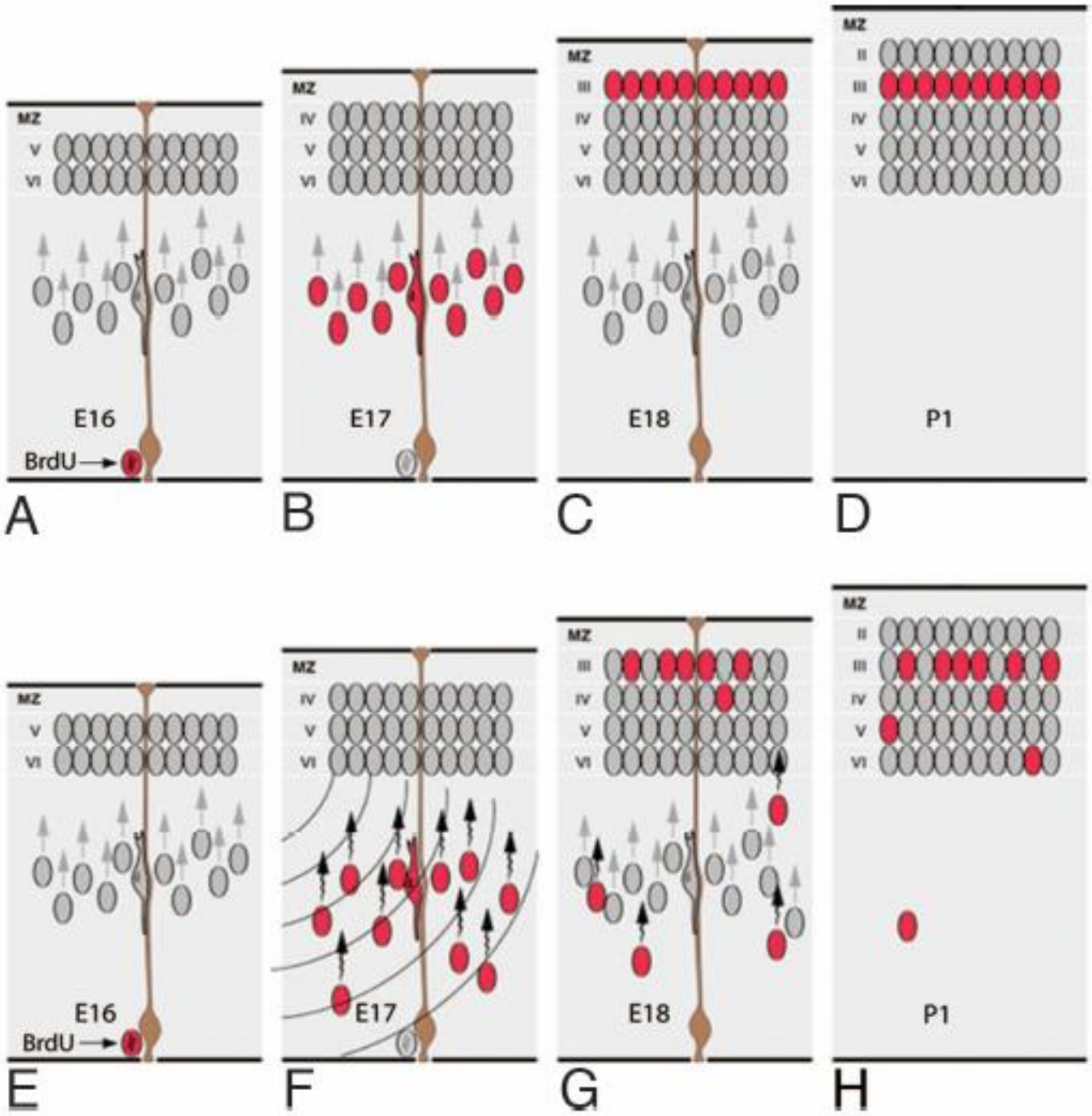


An epigenetic defect can give the same phenotype as a genetic defect

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