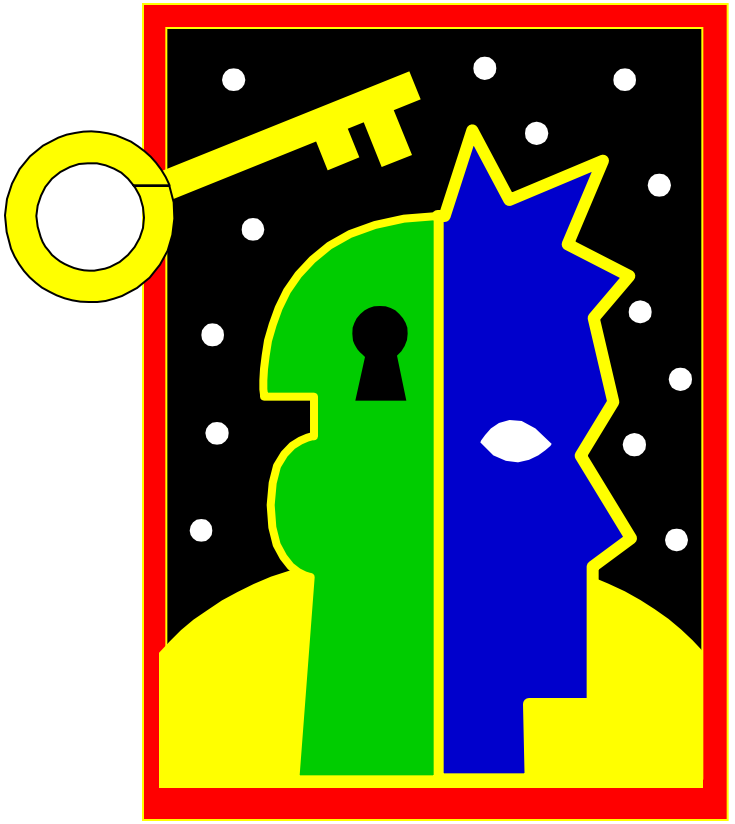
Sporadic schizophrenia

Beyond genetics…



Dolores Malaspina, M.D., M.P.H.
Anita Steckler & Joseph Steckler Professor of Psychiatry
NYU-Bellevue Department of Psychiatry

Creedmoor Psychiatric Center, NY State OMH
Adjunct Professor of Clinical Psychiatry,
Columbia University

Objectives

1. Describe new knowledge about the genetic heterogeneity of schizophrenia.

2. Describe the association between advancing paternal age and risks for psychiatric diseases.

3. Explain how gene expression is regulated by epigenetic mechanisms.

I have no conflicts of interest

Risk Factors for Psychosis

Maternal medical conditions:

pre-eclampsia, diabetes

Prenatal Exposures:

infection (influenza, rubella)

Malnutrition

stress (war, flood)

Rh incompatibility

Season of Birth

Obstetric conditions:

especially hypoxia
low birth weight
preterm birth

Childhood / adolescence

Cannabis

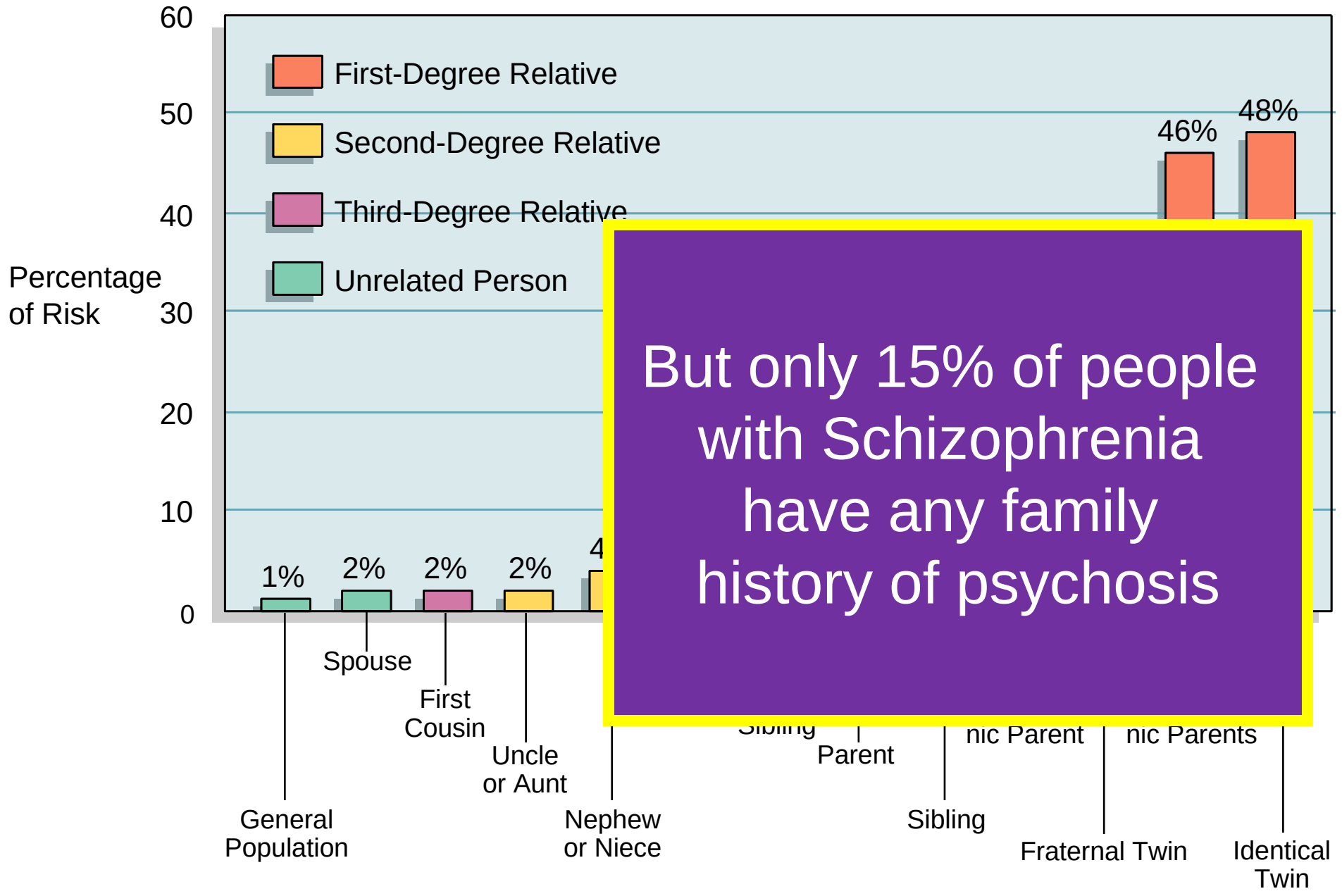
Traumatic brain injury

Trauma, loss, stress

Environmental Exposure:

Urban birth
Migration
Lead Exposure
Dry cleaning PERC

Family History is a Risk Factor for Psychosis



The case of the “Missing Heritability”

If schizophrenia is mainly genetic,

how is it maintained in the population,

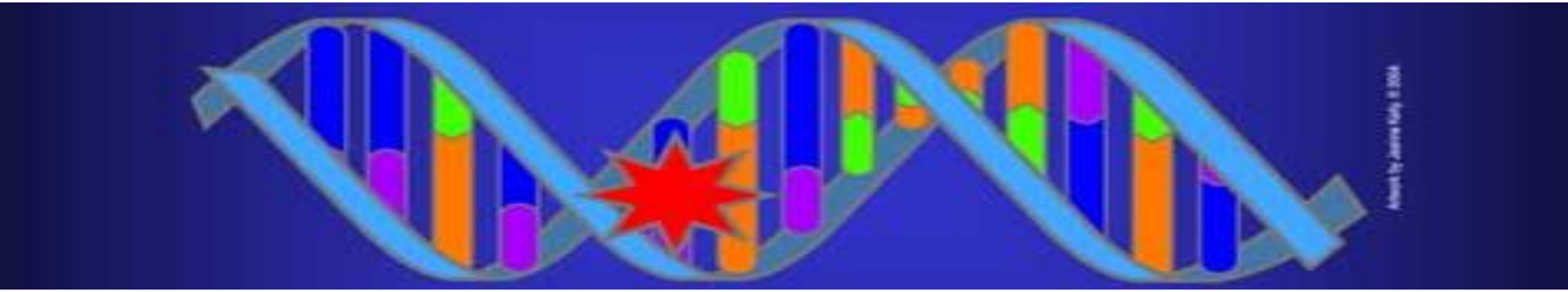
since those with the disorder have

far fewer children

It was know 100 years ago that the risk for sporadic genetic diseases was increased in the offspring of older parents

Could de novo mutations contribute to the risk for schizophrenia

Do new mutations cause schizophrenia



New mutations were proposed as a source of the disease a half century ago

The necessary mutation rates were considered to be too high to account for its prevalence.

Most mutations arise in the male parent

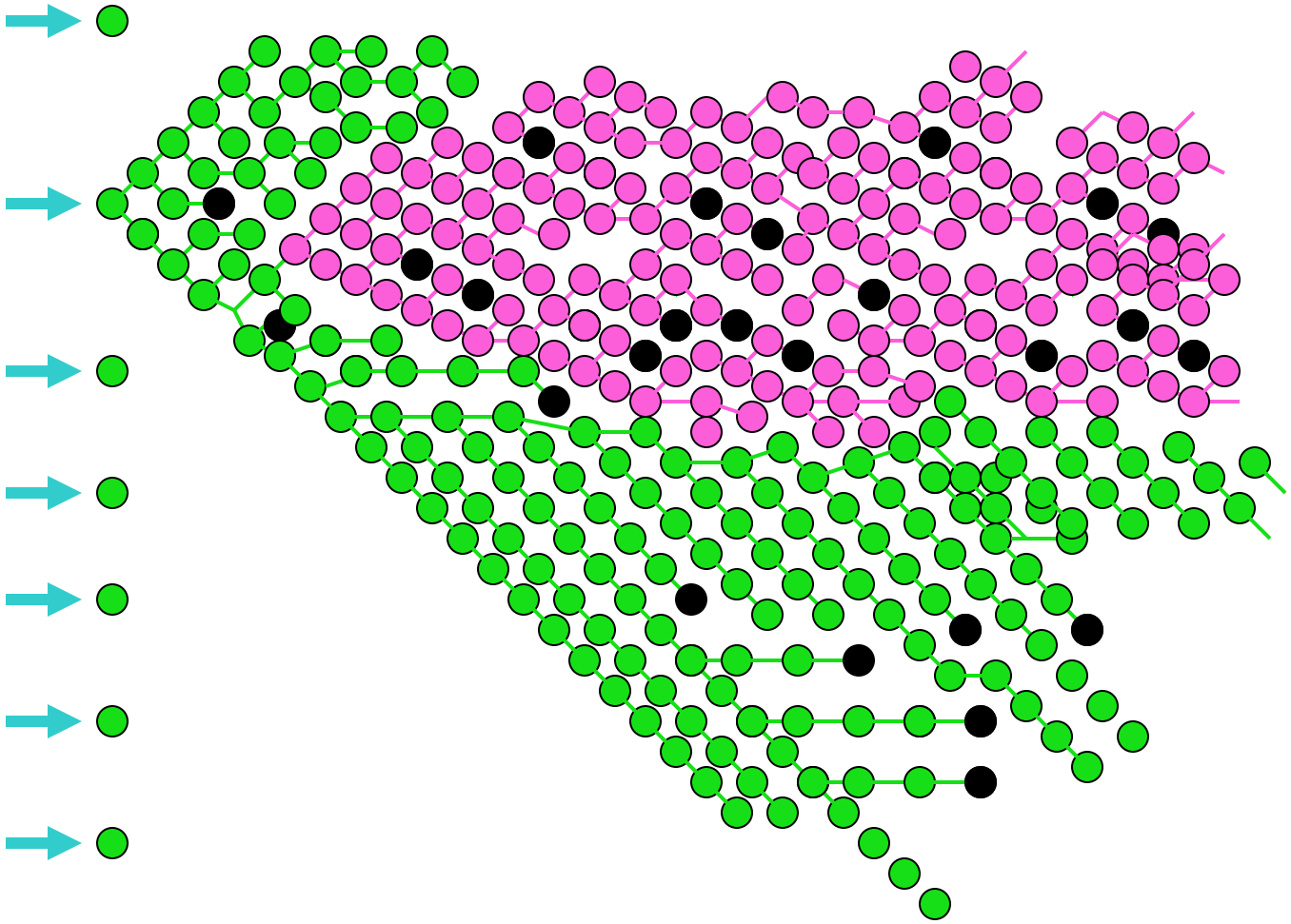
As in other mammals, new mutations in humans arise in the continually replicating male germ line (Penrose, 1955).

In women, oocytes are formed before birth. There are 24 divisions, all but the last occurs during fetal life.

In men, spermatogonia divide every 16 days

→ 200 times by age 20
→ 660 by age 40

The proportion of sperm with mutations increase with the age of the male parent



Several groups had found older fathers or late birth order in schizophrenia patients

(Johanson 1958; Gregory 1959; Farina 1963; C Schooler 1964; Bojanovsky & Gerylovova 1967; Hare & Moran 1979; Kinnell 1983; Bertranpetit & Fananas 1993...)

They were interpreted as reflecting a late marriage age for psychiatrically vulnerable parents or the result of methodological difficulties.

These well replicated findings were used to support the hypothesis that maternal unavailability and family environment contributed to schizophrenia.

Mutations from older fathers & heritable disease

Autosomal Dominant:

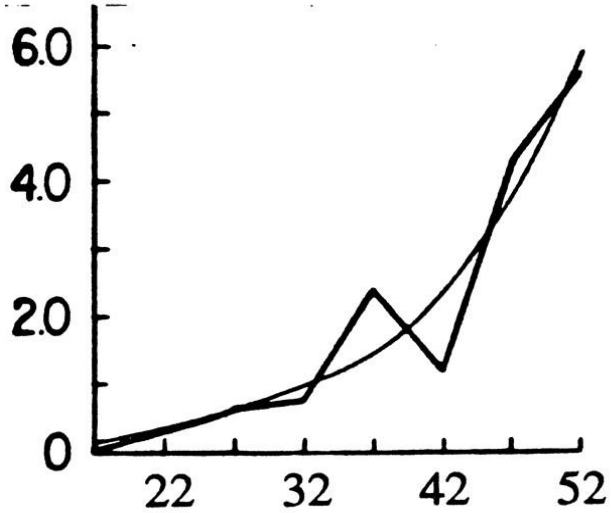
Achondroplasia, Neurofibromatosis, Marfan Syndrome, Osteogenesis Imperfecta, Apert,, Cruzen, and Pfeiffer Syndrome…..

X-linked conditions,

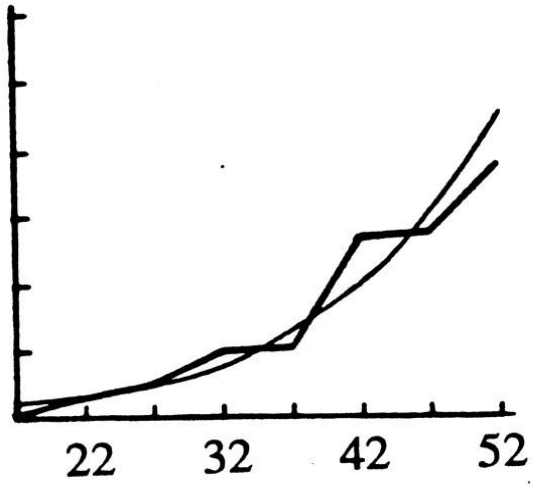
Fragile X syndrome, Hemophilia, Muscular Dystrophy…

Complex Disorders:

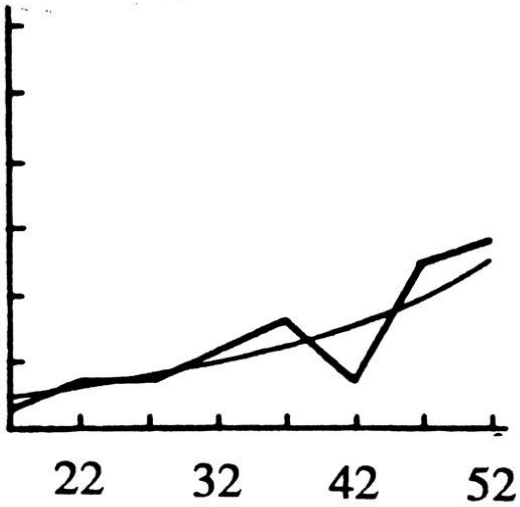
Congenital Heart Defects, Neural Tube Defects, Mental Retardation, Cerebral Palsy, Prostate Cancer, Retinoblastoma, Wilms Tumor, Renal Agenesis, Progeria, Torsion Dystonia, Alzheimers Disease…



Apert syndrome



Achondroplasia



Neurofibromatosis

Jerusalem Perinatal Cohort Study:

A prospective population birth cohort study of all ~100,000 births in Jerusalem:1964-1976

Pregnancy complications and events

Cohort data cross-linked to Israel's Psychiatric Case Registry

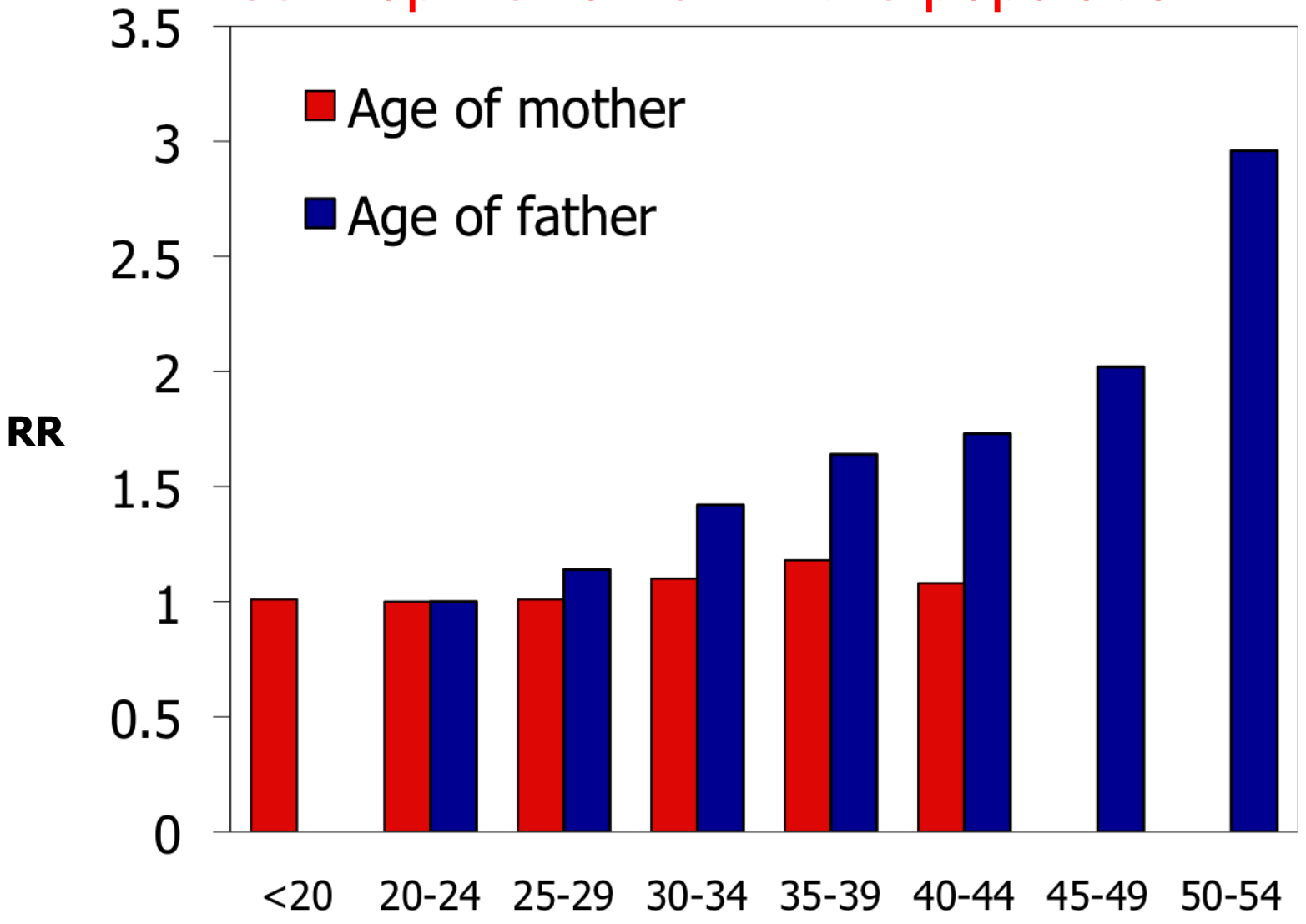
Preconception

Life events after delivery

Outcomes

Time

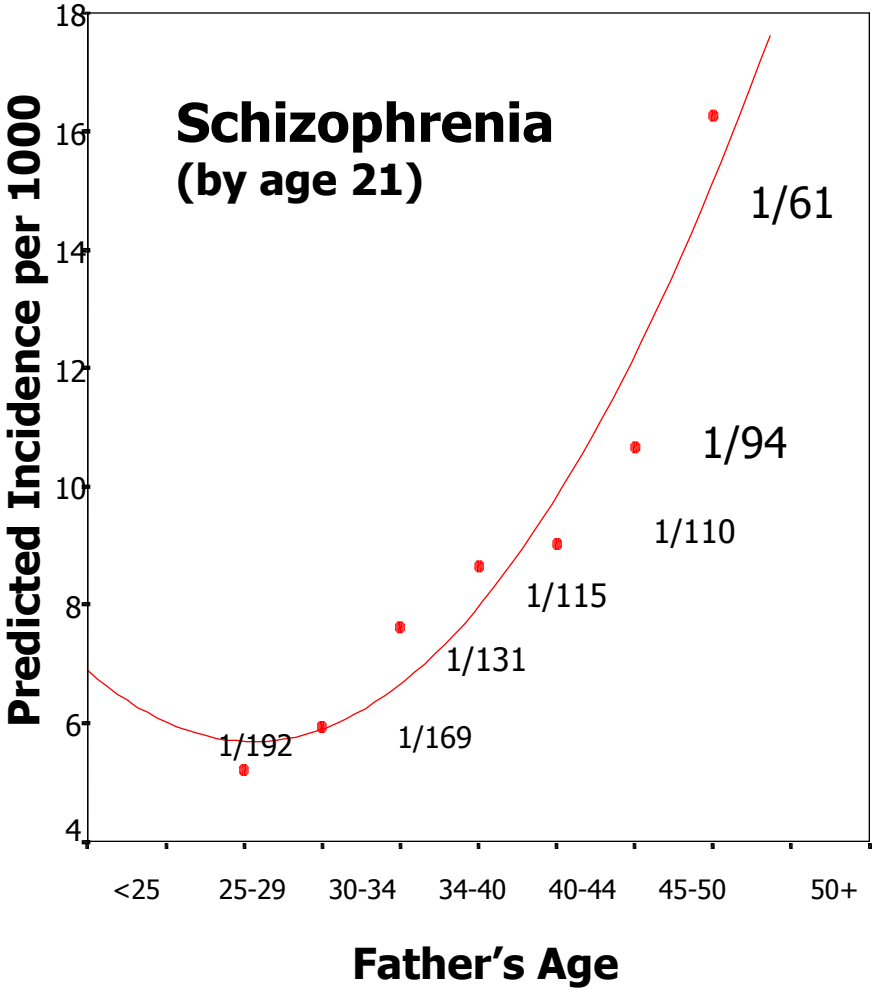
Paternal age accounted for a quarter of schizophrenia risk in the population

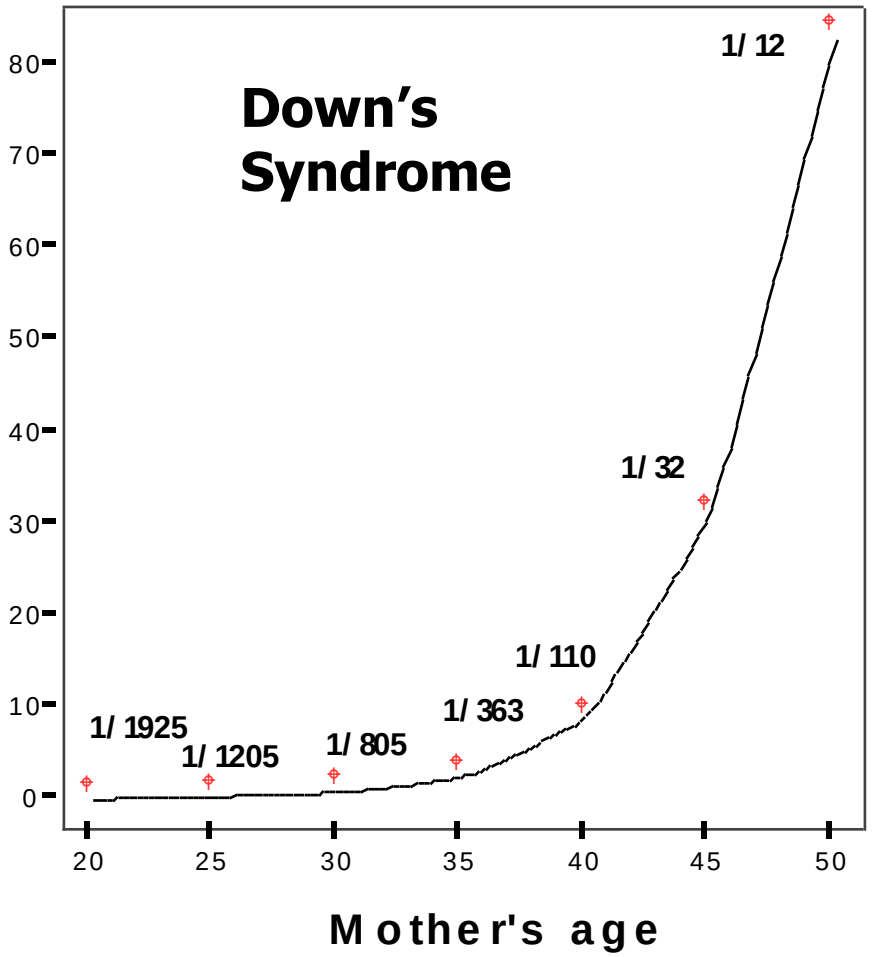


Parental birth age, in years, corrected for other parent's age

Malaspina 2001

Schizophrenia and Paternal Age versus Downs Syndrome and Maternal Age





Malaspina et al, 2002

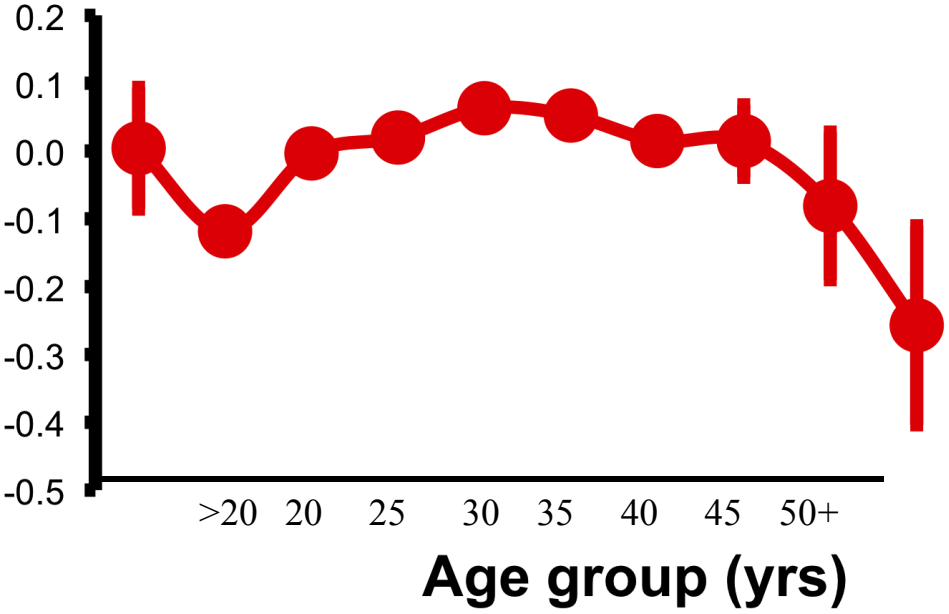
Supportive evidence from military data on healthy adolescents, APA IQ and paternal age

- reduced performance IQ with preserved verbal IQ

Malaspina et al 2005

- significantly lower social competency scores

Weiser et al, 2008

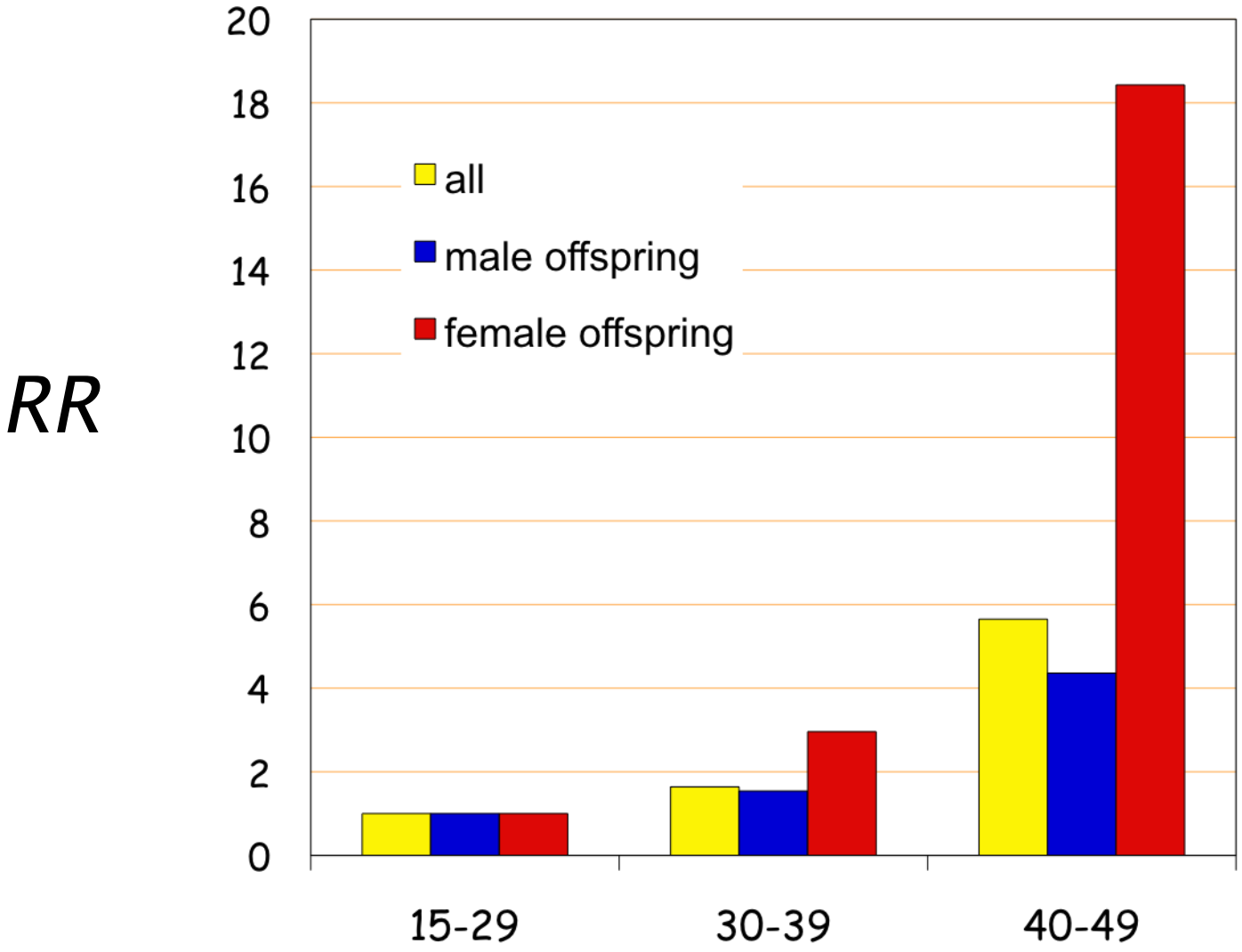


With later paternal age:

-lower nonverbal IQ

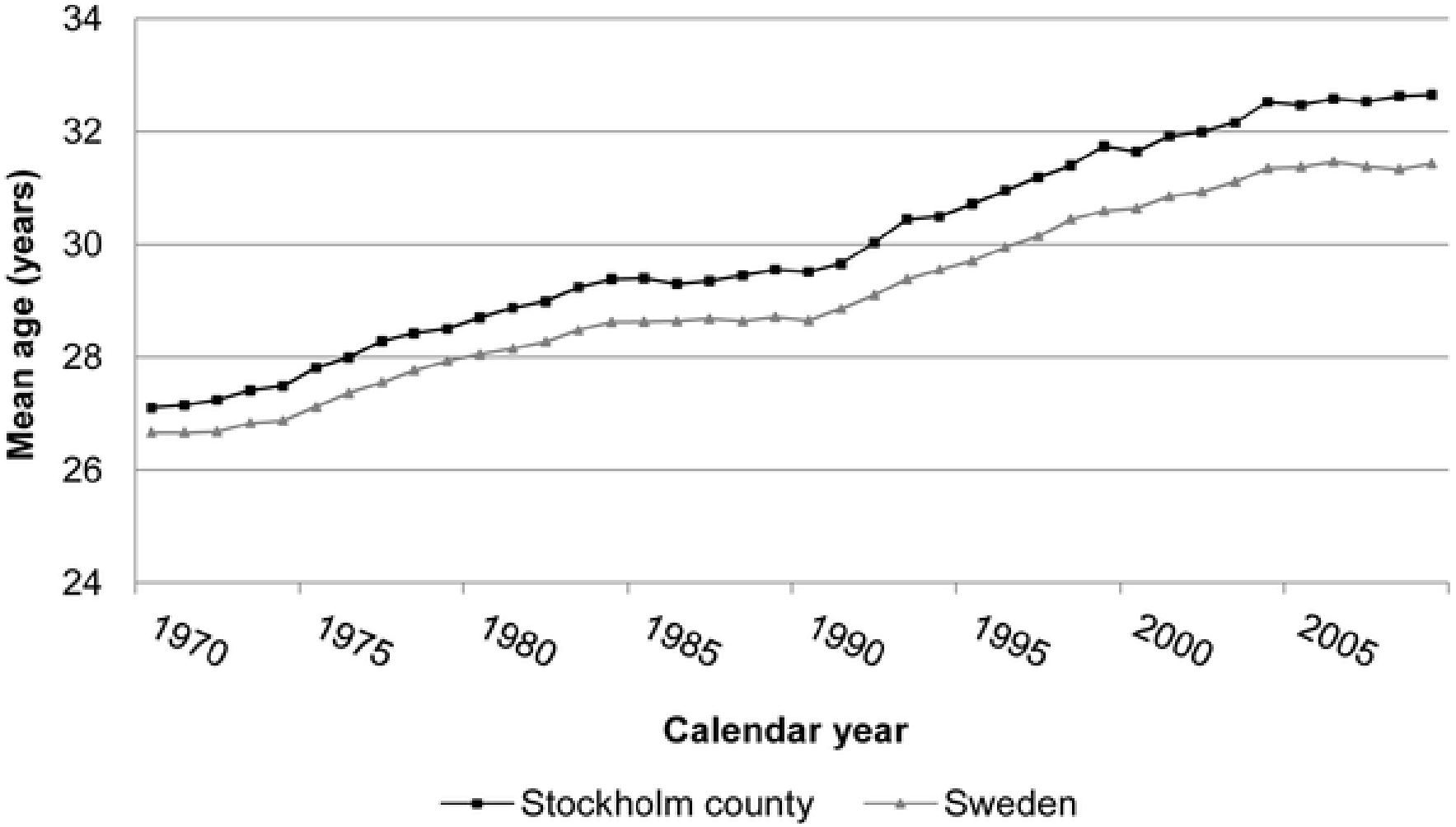
-no effect on verbal IQ

Paternal age was related to autism and explained in the increased risk for autism in Israel



Reichenberg et al, 2006

Trends in paternal mean age at first child birth in Sweden and Stockholm County, 1970–2009



Svensson AC, Abel K, Dalman C, Magnusson C (2011) Implications of Advancing Paternal Age: Does It Affect Offspring School Performance?. PLoS ONE 6(9): e24771. doi:10.1371/journal.pone.0024771
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0024771

Paternal exposures could increase point mutations in spermatozoa

Ionizing radiation exposure

Free radicals and oxidative stress

Decreased DNA repair enzymes

Arteriosclerosis

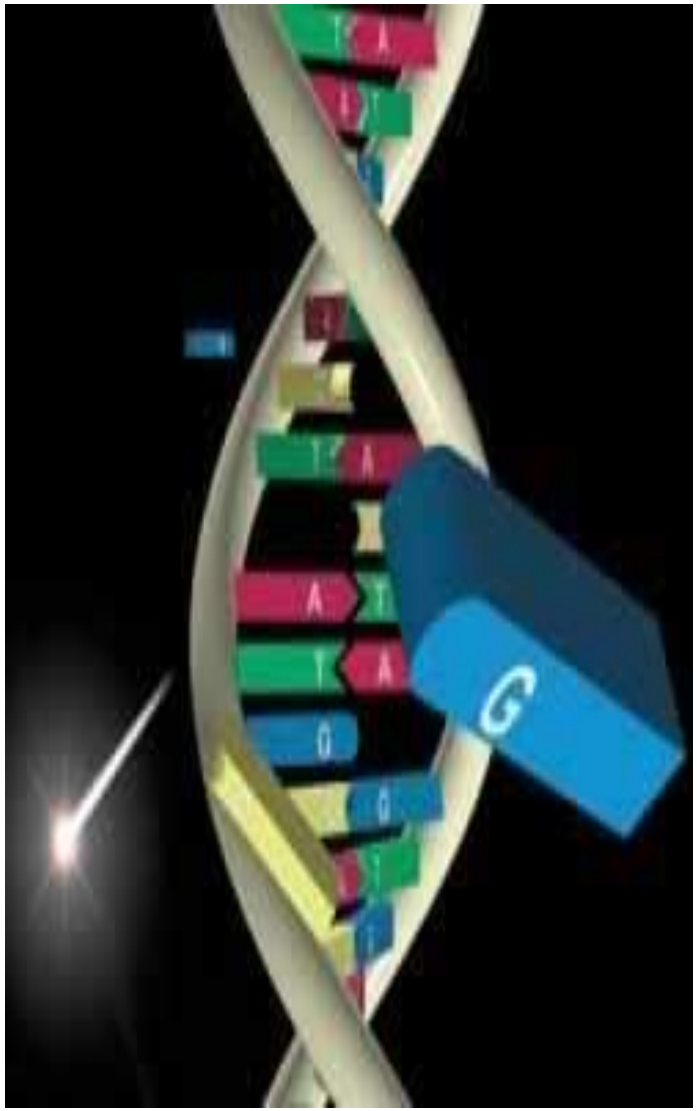
Nutritional deficiencies

Smoking, Alcohol, Narcotics

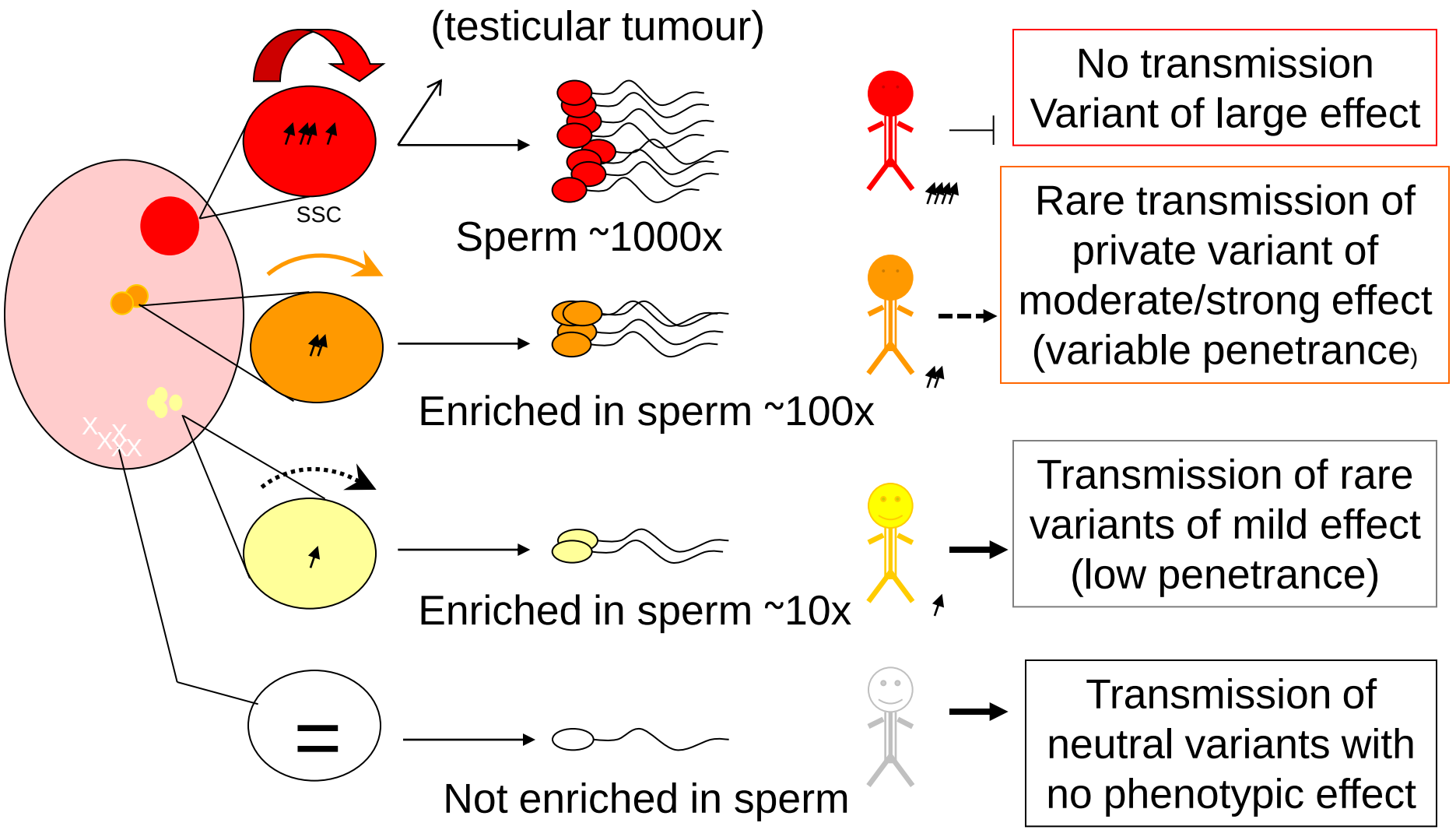
Lead, cadmium, anesthetic gas

Agent orange ? , estrogen ?

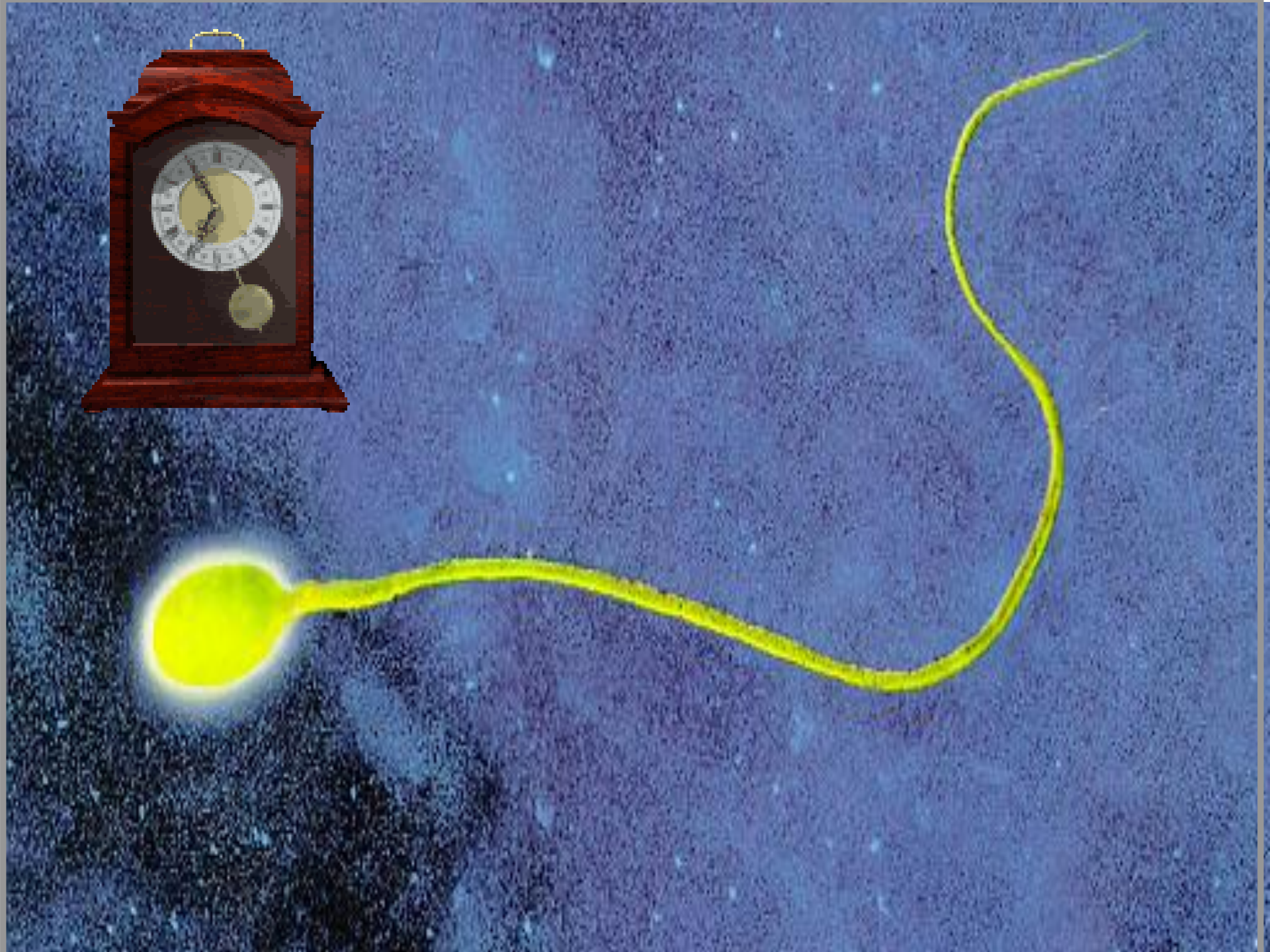
Hyperthermia



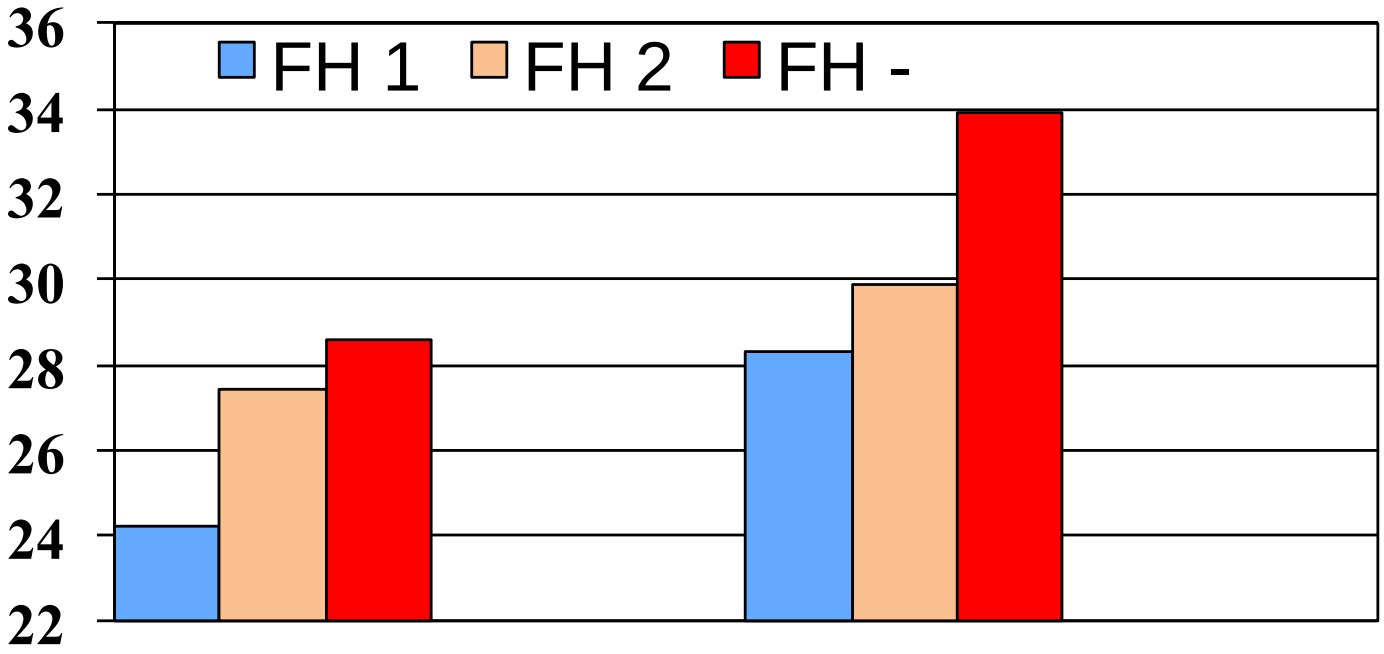
Mutation → selection → reproduction → germline trasnmission



Accumulation of private neutral variations + pathogenic variants with mild effects occurs over several generations through selection



Parents of cases with a family history were actually younger than sporadic cases

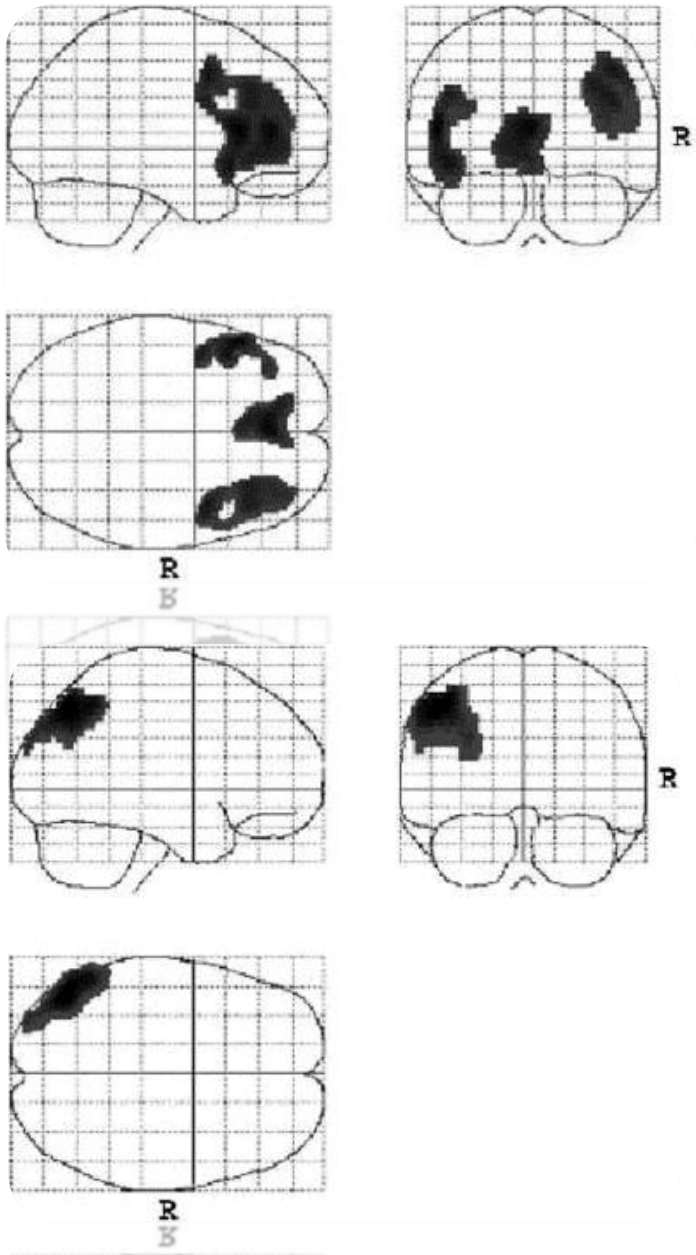


Mother	**1st degree**	**(16)**	**24.3 (5.1)**	**Father**	**1st degree**	**(16)**	**28.3 (5.5)**
	2nd degree	**(16)**	**27.4 (7.3)**		**2nd degree**	**(16)**	**29.9 (7.3)**
	none	**(64)**	**28.6 (6.1)**		**none**	**(64)**	**33.9 (8.5)**

ANOVA maternal & paternal ages by group: F=3.15, p=.047;F=3.87, p=.02.

Malaspina et al 2002

Regions of decreased perfusion



Sporadic Schizophrenia

Middle, inferior, orbital PFC
anterior cingulate and insula
paracingulate cortices

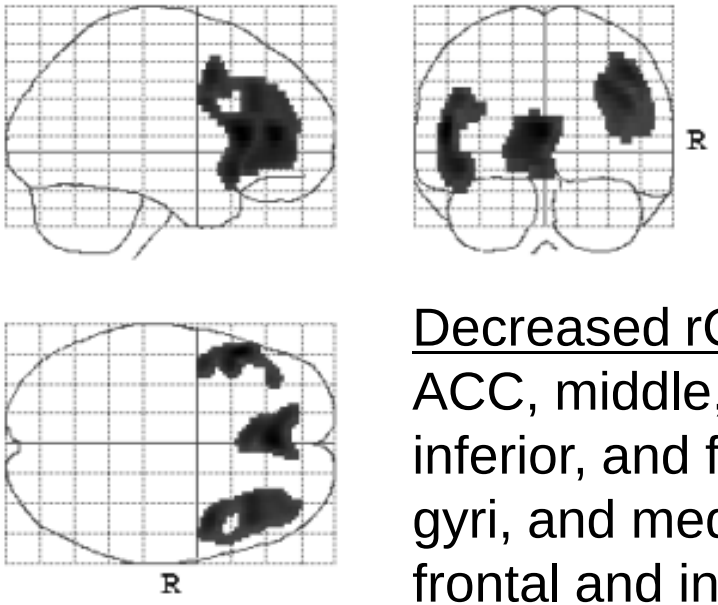
Familial Schizophrenia

Superior & inferior parietal lobule, gyri of the middle & superior temporal lobe.

COMPARING GROUPS:
Sporadic cases had lower rCBF in left anterior cingulate and medial frontal gyrus than familial cases.

Malaspina et al, 2004

For PARS vs. healthy controls



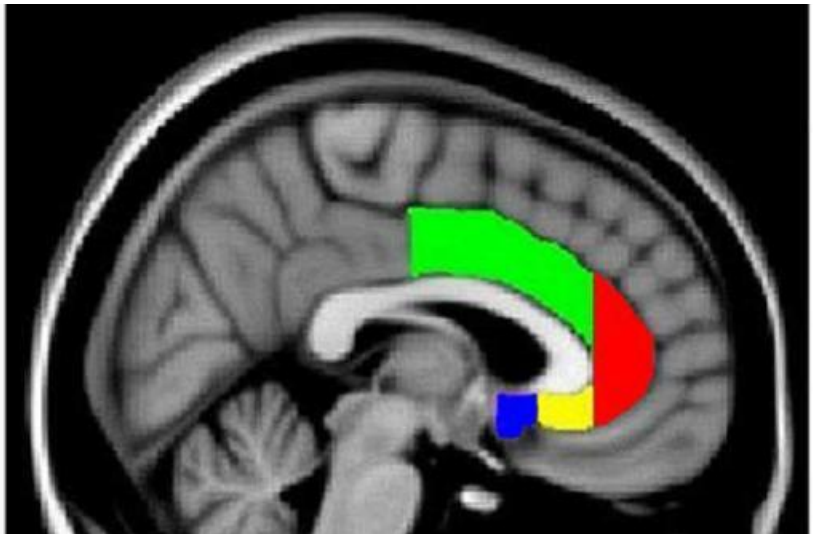
Decreased rCBF:
ACC, middle, inferior, and frontal gyri, and medial frontal and insula.

Malaspina et al 2005

MRS: SZ cases vs controls

Deficit in rostral concentrations of neurons in rostral vs caudal Anterior Cingulate Cortex.

- 68% sensitive and 91% specific for cases vs controls.



Subregions of the ACC.
Red: rostral
Green: caudal

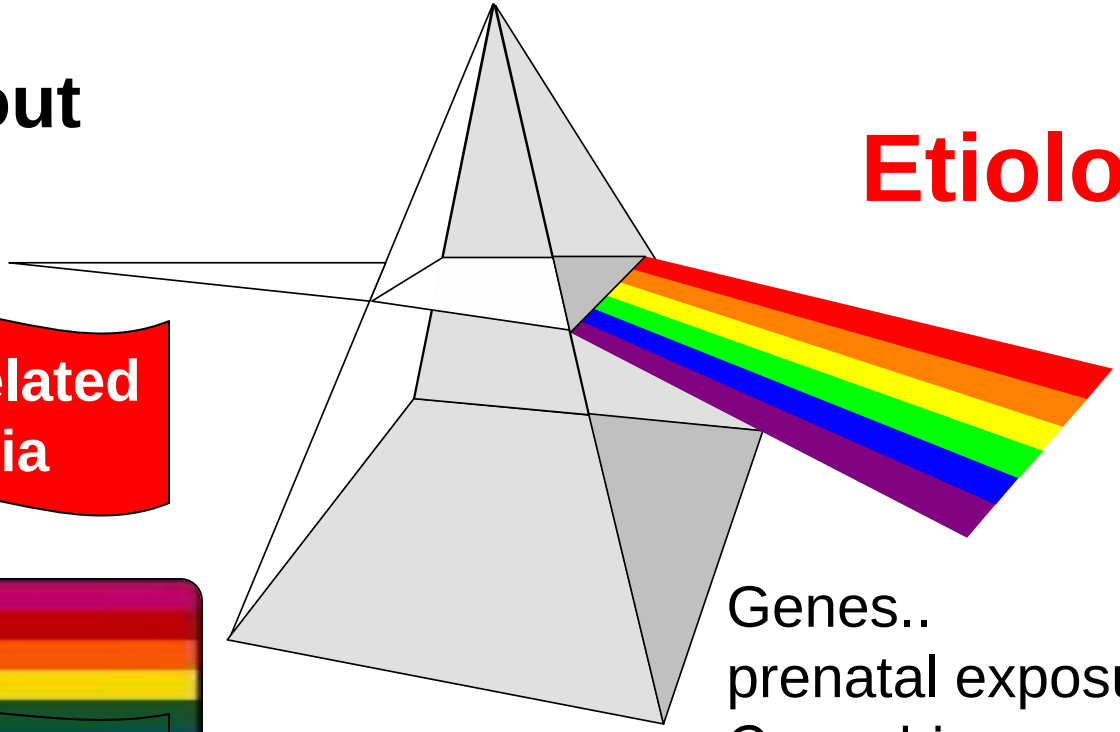
Hardy et al 2011

Chronic Psychosis: Syndrome with many causes

Separating out Subtypes

Paternal Age Related Schizophrenia

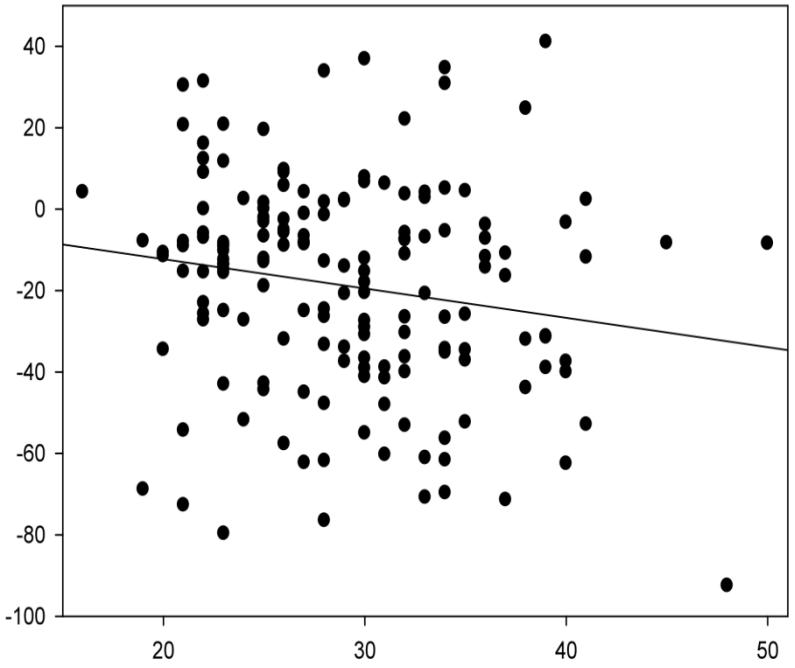
Other Schizophrenia



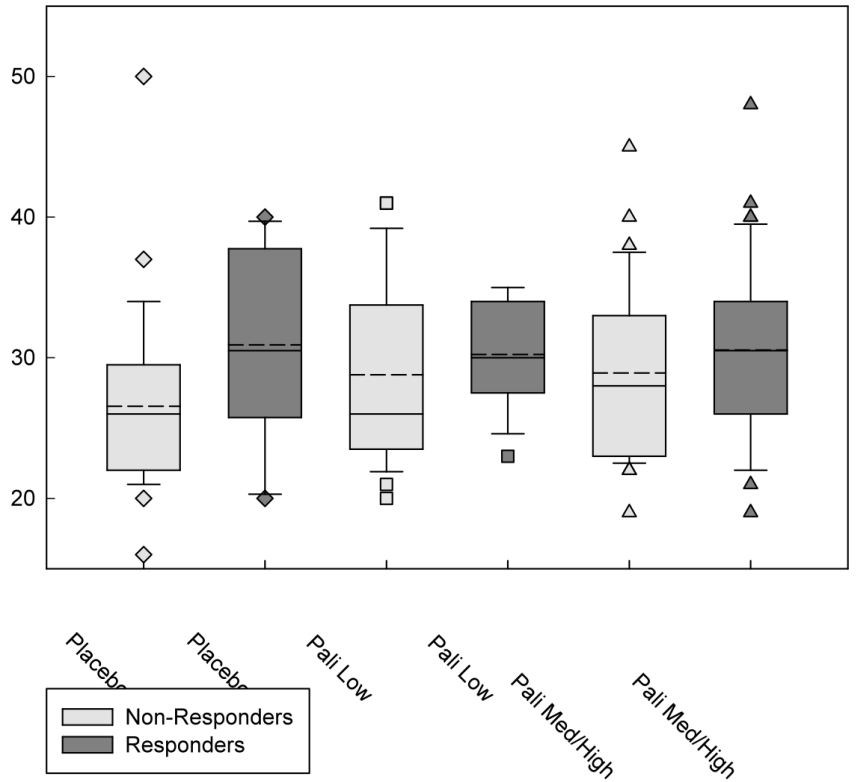
Etiologies

Genes..
prenatal exposures..
Cannabis…
Traumatic brain injury.
obstetric complications..
Stress sensitivity
stress..
infectious agents…

Advancing paternal age predicts better treatment response in 200 adolescents with schizophrenia



Intent to treat analysis
R =-0.17; p = 0.02; n = 160



Older paternal age for responders (≥20% symptom reduction) than non-responders

Opler, Malaspina et al, in press

The findings support the idea that paternal age Is an etiology for a specific type of schizophrenia

Fathers age was related to treatment response in psychotic adolescents, but not to onset age or initial symptom severity.

This study provide evidence of differential treatment response in association with etiology in adolescents with older parents.

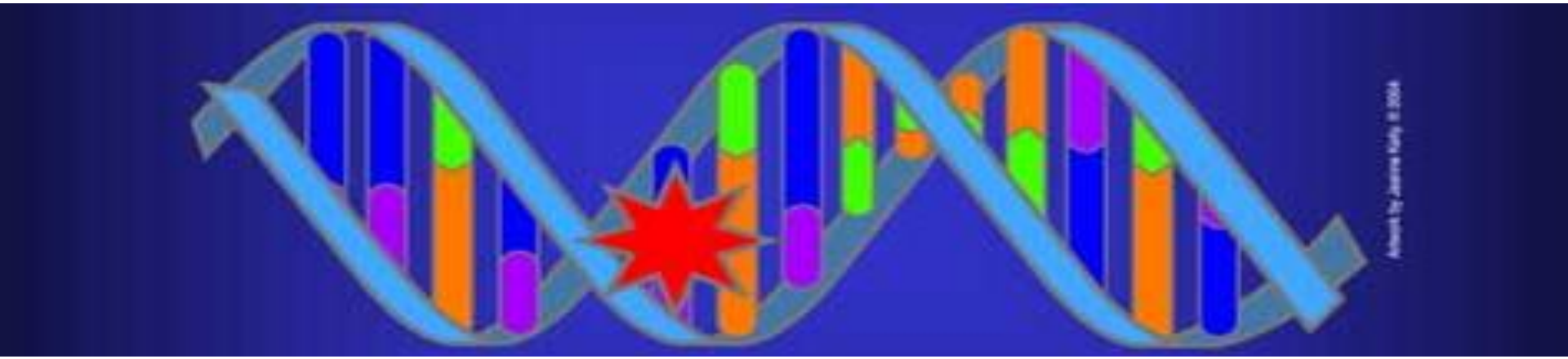
The data supports the hypothesis that parental ages produce a subtype in the offspring that is more treatment responsive.

Paternal age was significantly correlated to improvement in positive symptoms and maternal age significantly related to negative symptoms

Overall correlations were small, but significant, and have the potential to impact treatment effects when applied to larger populations and longer treatment durations.

In the Jerusalem Cohort:

Half of the cases without a family history had a mutation in a gene that was not present in their mother of father. (Malaspina unpublished)



Do paternal life-course exposures play a role?

Telomere Lengths

Telomeres are the protective caps at the end of chromosomes.

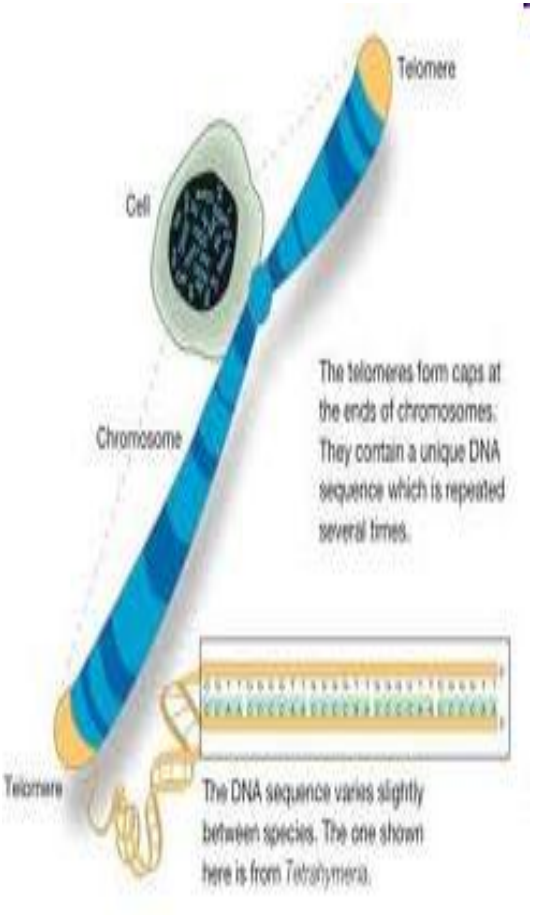
Telomere length determines the number of cell divisions a stem cell can undergo.

Shortening of telomeres –> activates cell death. Risk for cardiovascular disease.

Cancer cells have this enzyme→ too long telomeres increase cancer risk

Telomeres are usually lengthened with later paternal age.

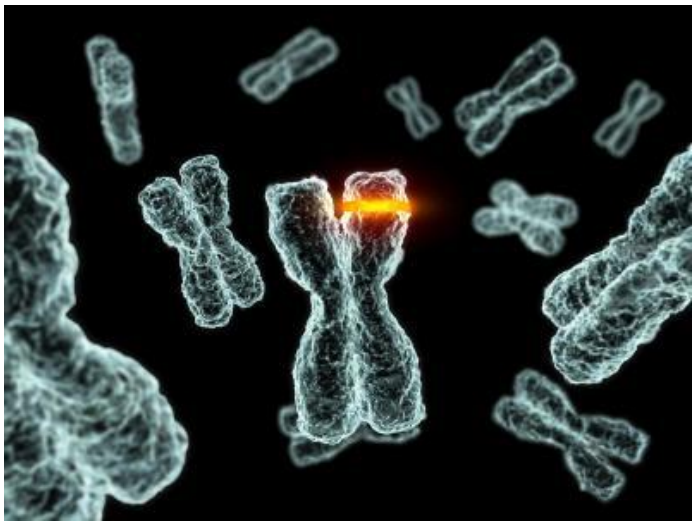
Are telomeres longer or shorter in schizophrenia?



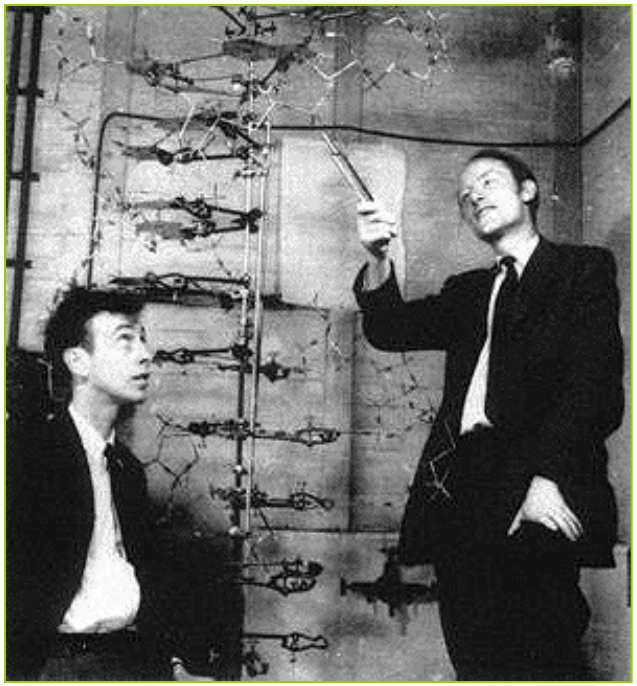
Copy Number Variation

CNV:

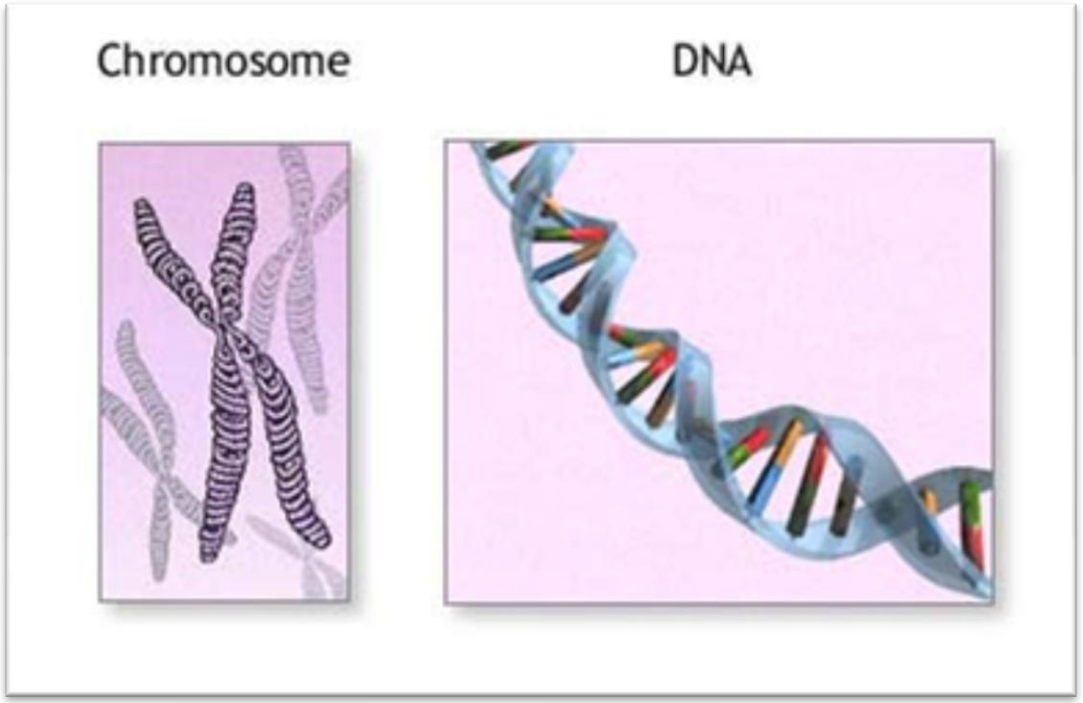
variation in number of copies from the normal two copies of each gene, or of large sequences of DNA, increased in the genome of individuals with psychiatric diseases?



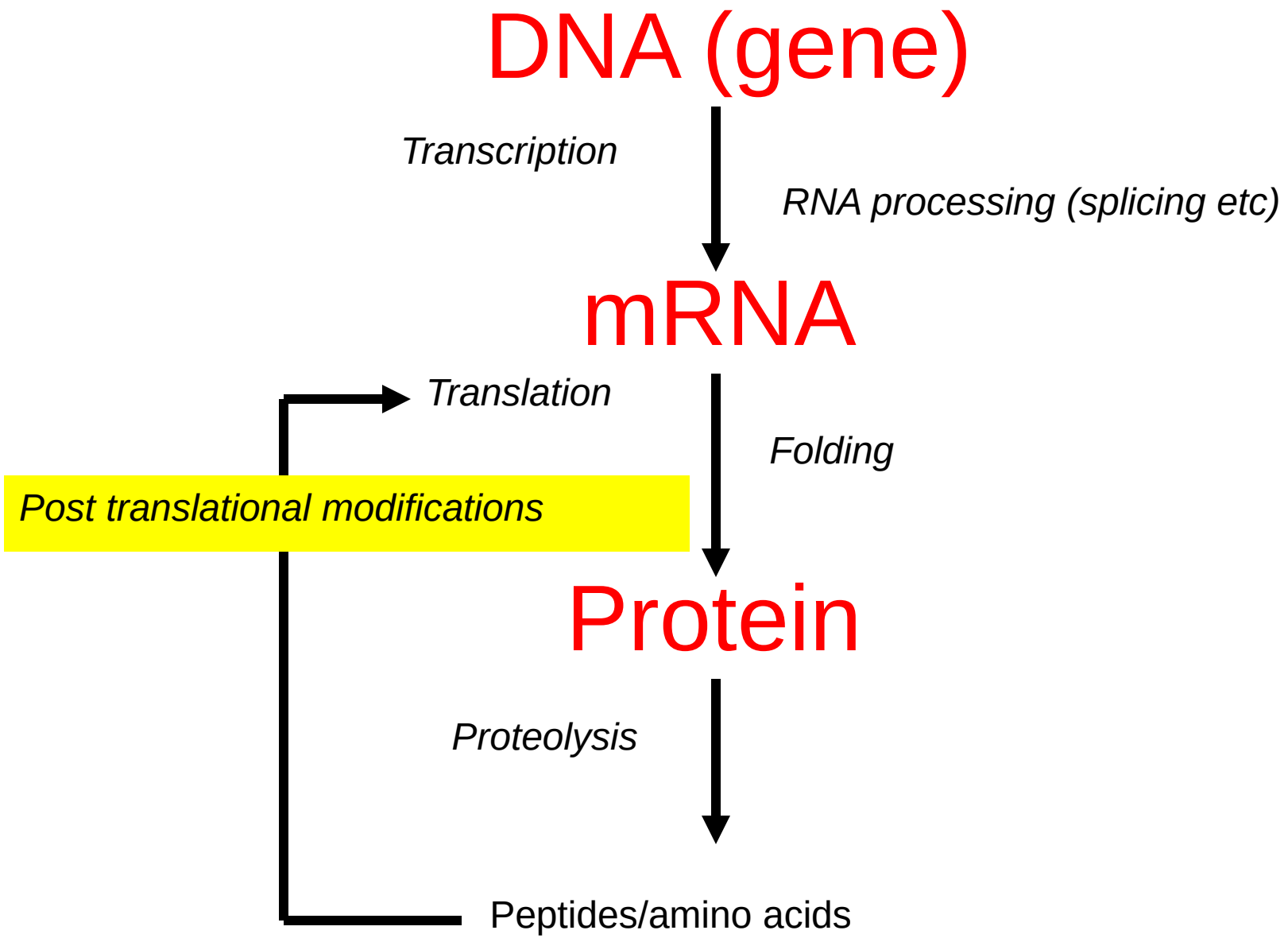
Modern Genetics



Francis Crick shows James Watson the model of DNA.

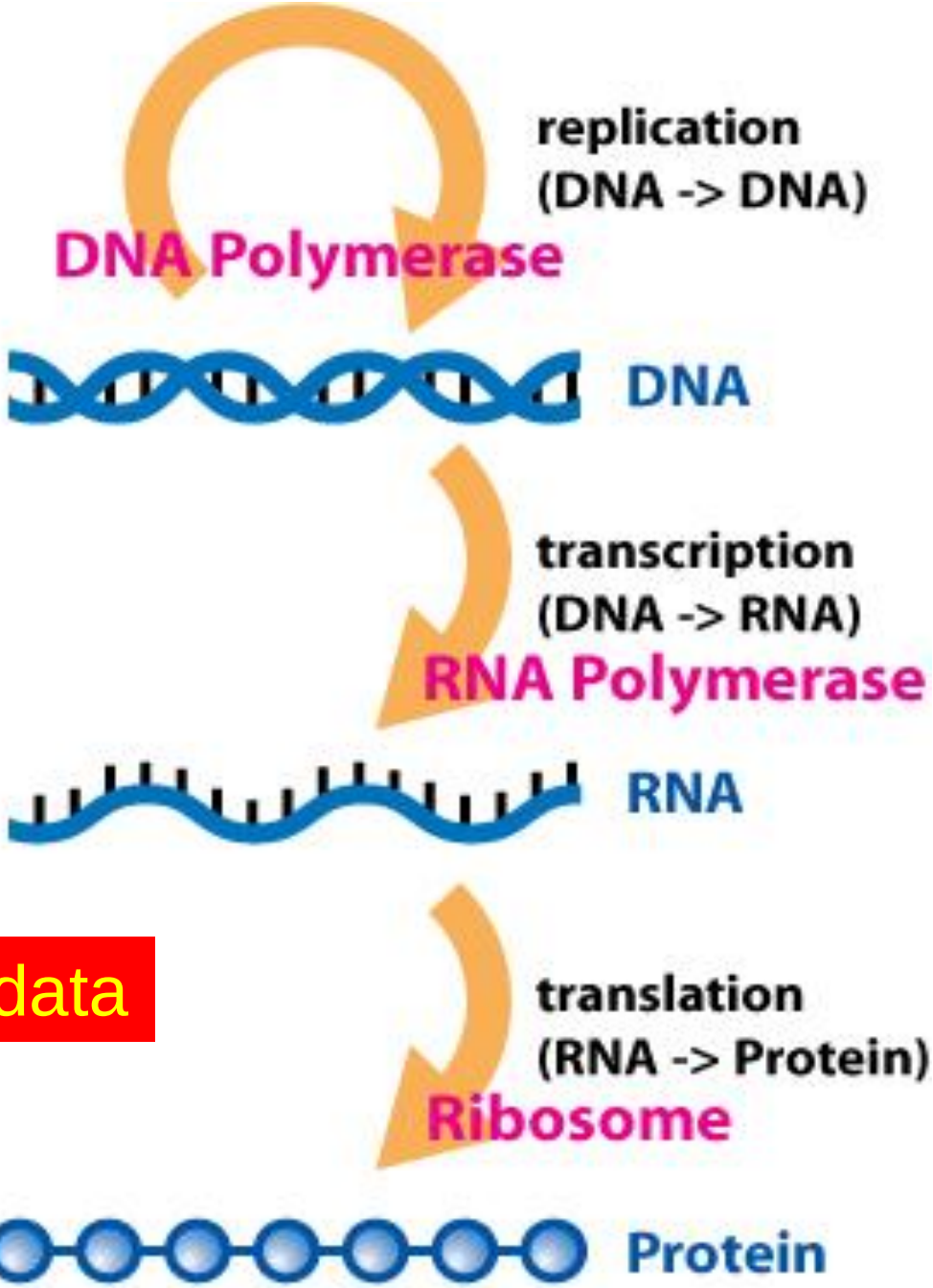


Rosalind Franklin used X-ray crystallography to study DNA structure


DNA (gene)
Transcription
RNA processing (splicing etc)
mRNA
Translation
Folding
Post translational modifications
Protein
Proteolysis
Peptides/amino acids

Central dogma of molecular biology

DNA → RNA → protein



Central dogma of molecular biology

No longer explains the data

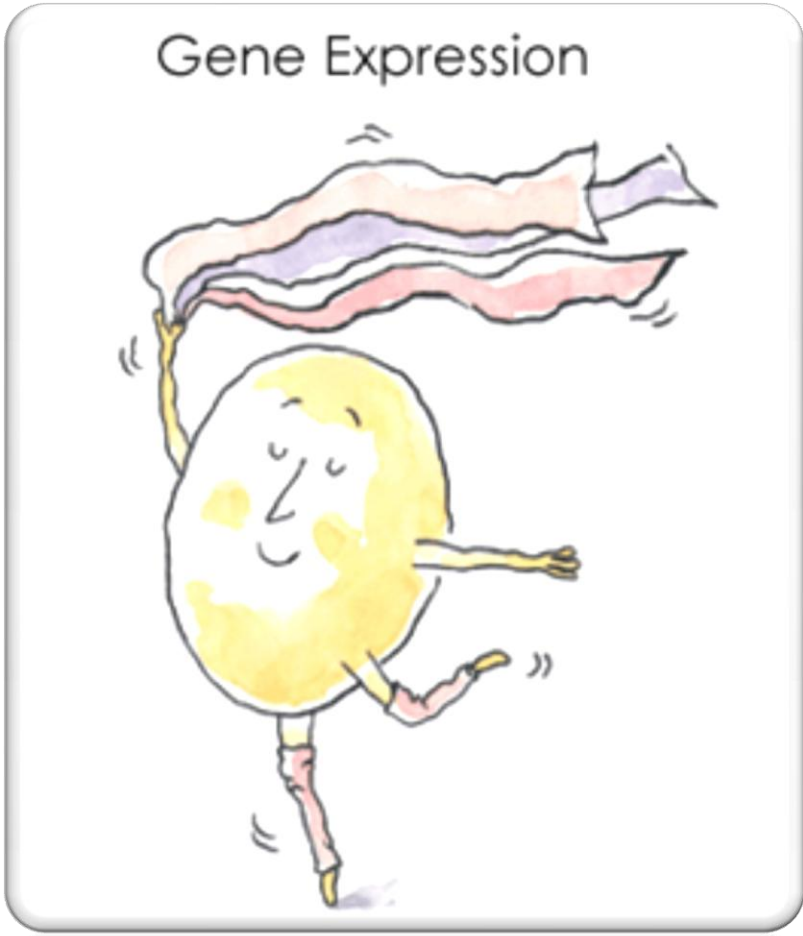
DNA → RNA → protein

Epigenetics

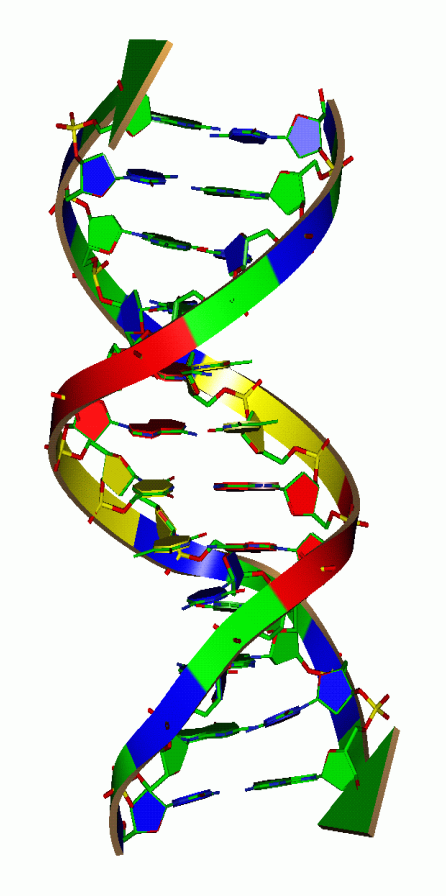
Epigenetic mechanisms control gene expression without altering the DNA sequence.

***Like DNA sequence,* epigenetic factors are critically important for cell functioning and some can be inherited.**

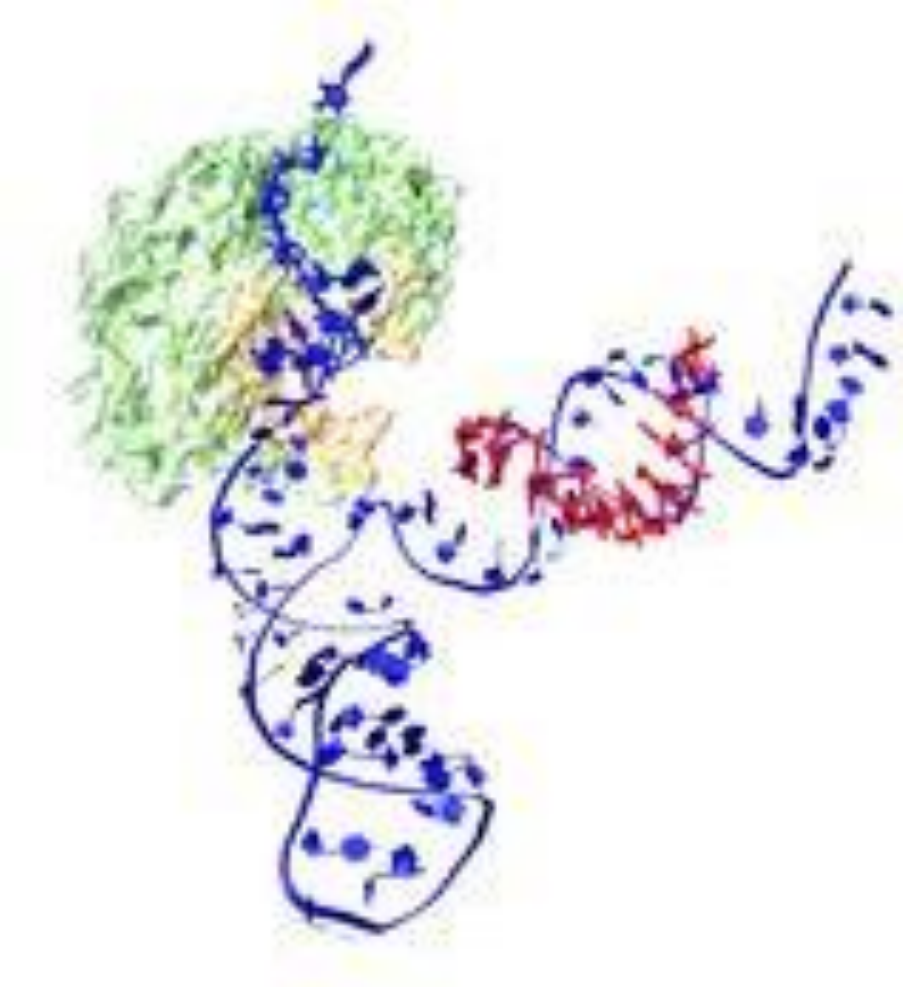
***Unlike DNA sequence,* epigenetic mechanisms can change during development, and some can derive from environmental exposures of the fetus, parents, and grandparents.**



Genetics → Epigenetics



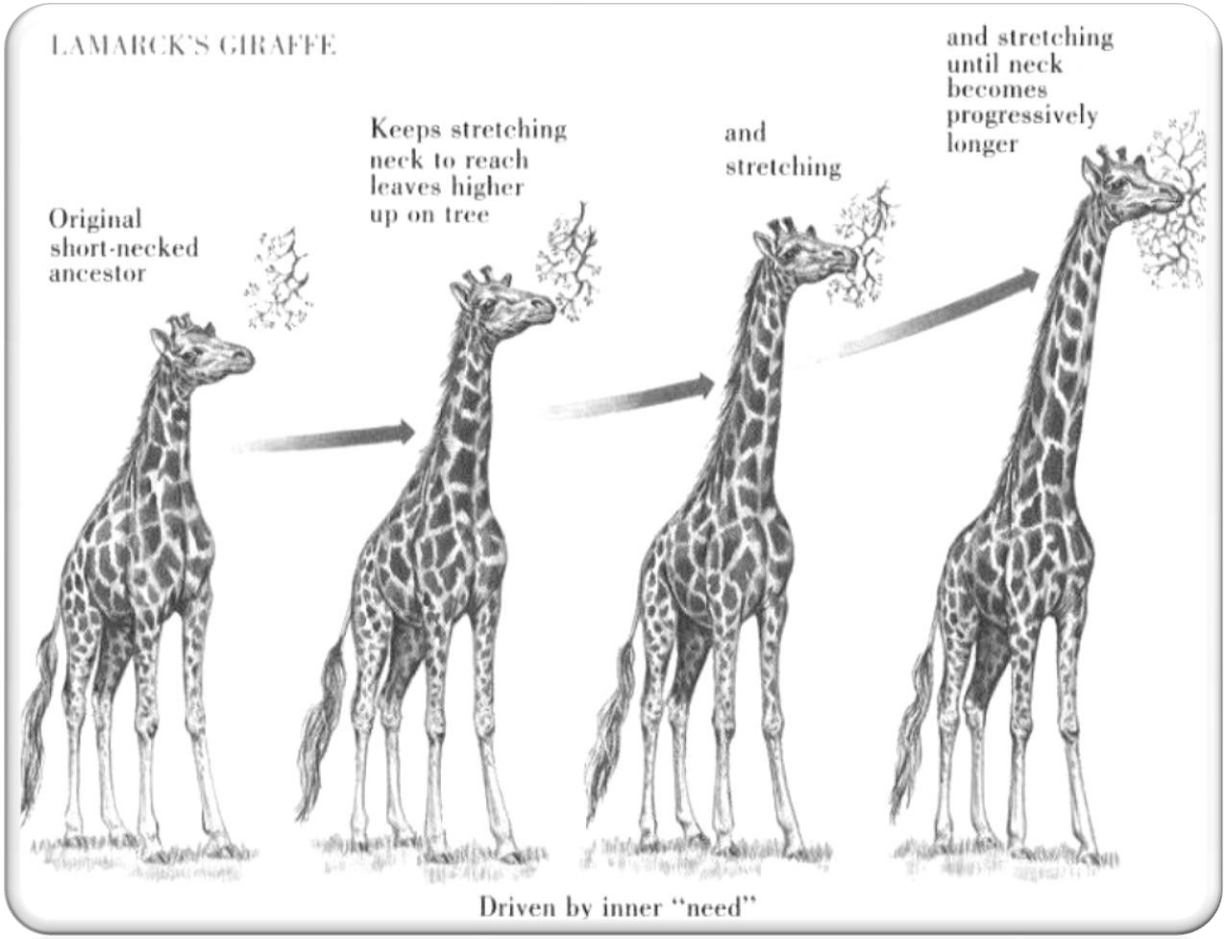
1953



2013

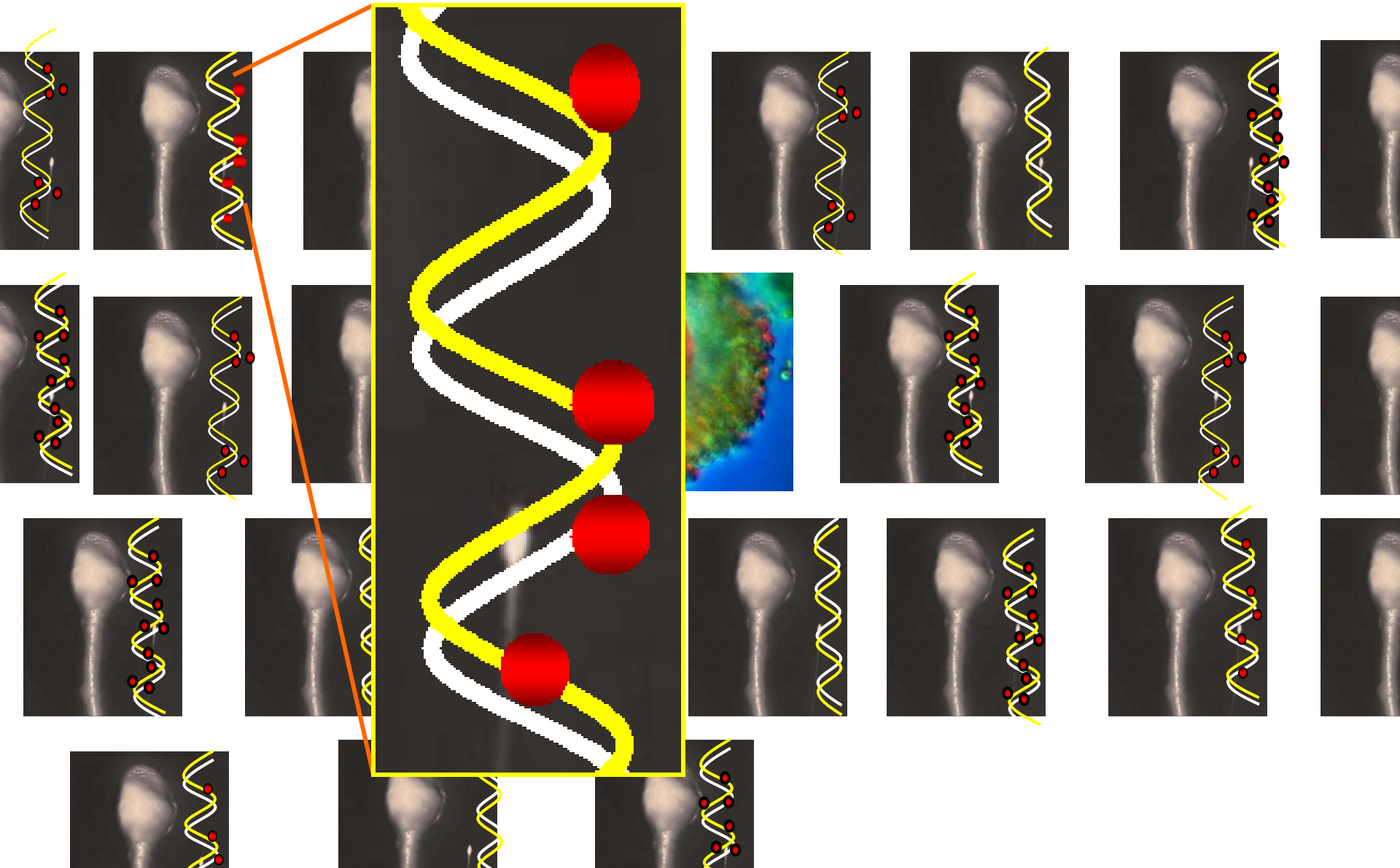
The Inheritance Of Acquired Traits

Jean-Baptiste Lamarck (1744–1829)



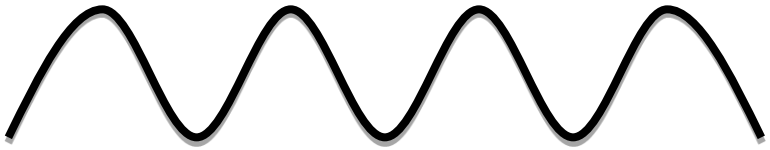
Darwin's *Origin of Species* did propose natural selection as the main evolutionary mechanism, but did not exclude a type of Lamarckism as well.

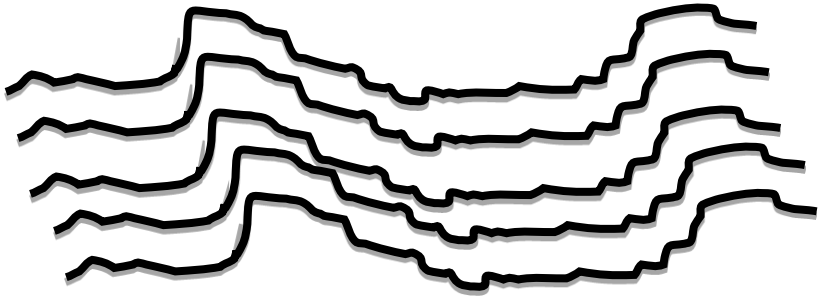
Epigenetic mechanisms can be inherited along with DNA sequences

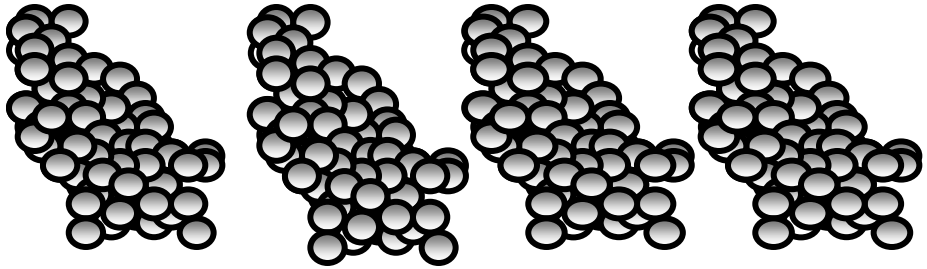


DNA methylation can decrease transcription

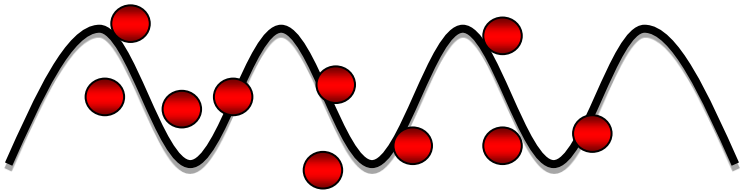
Scenario 'A'







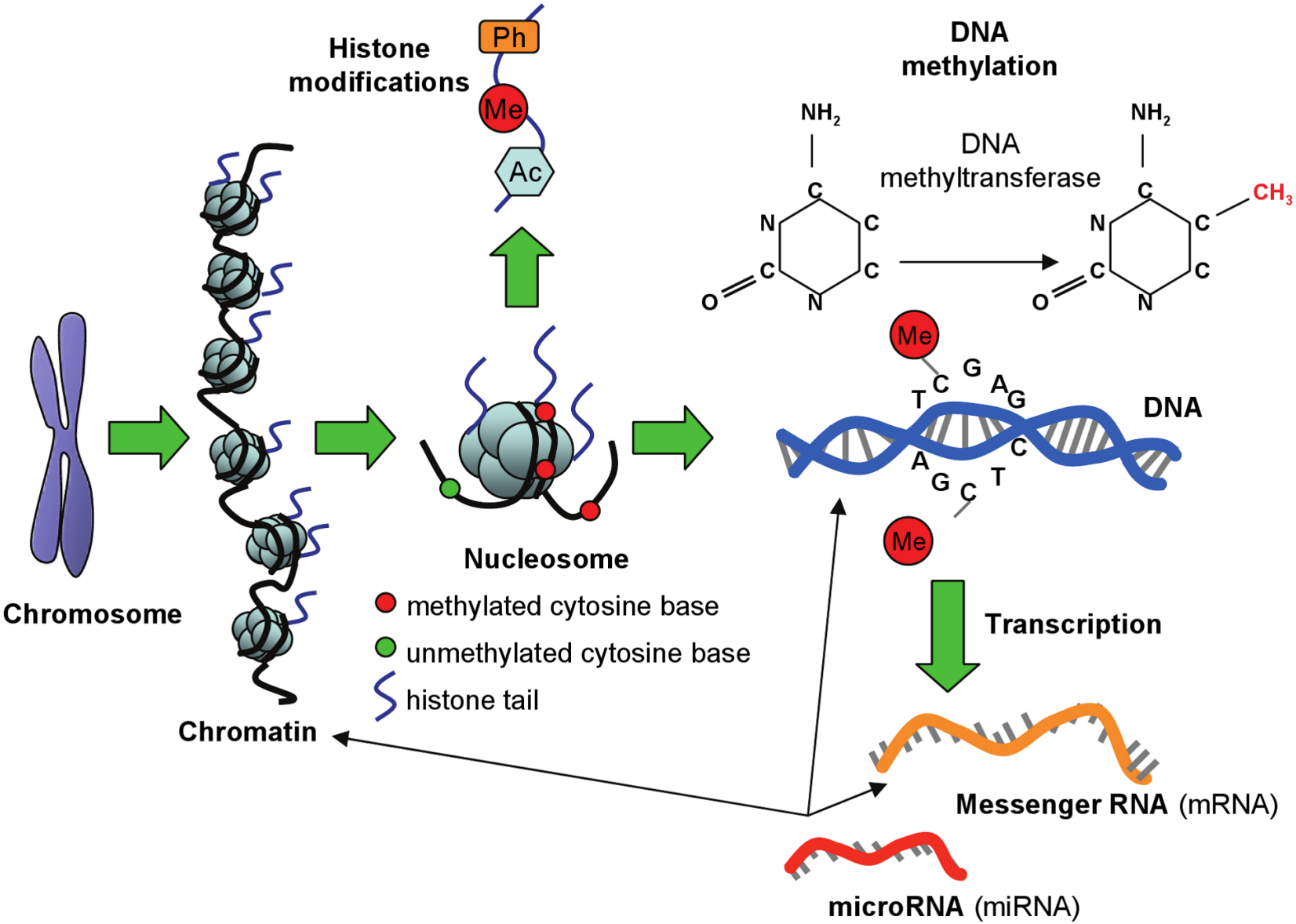
Scenario 'B' with methylation



No expression

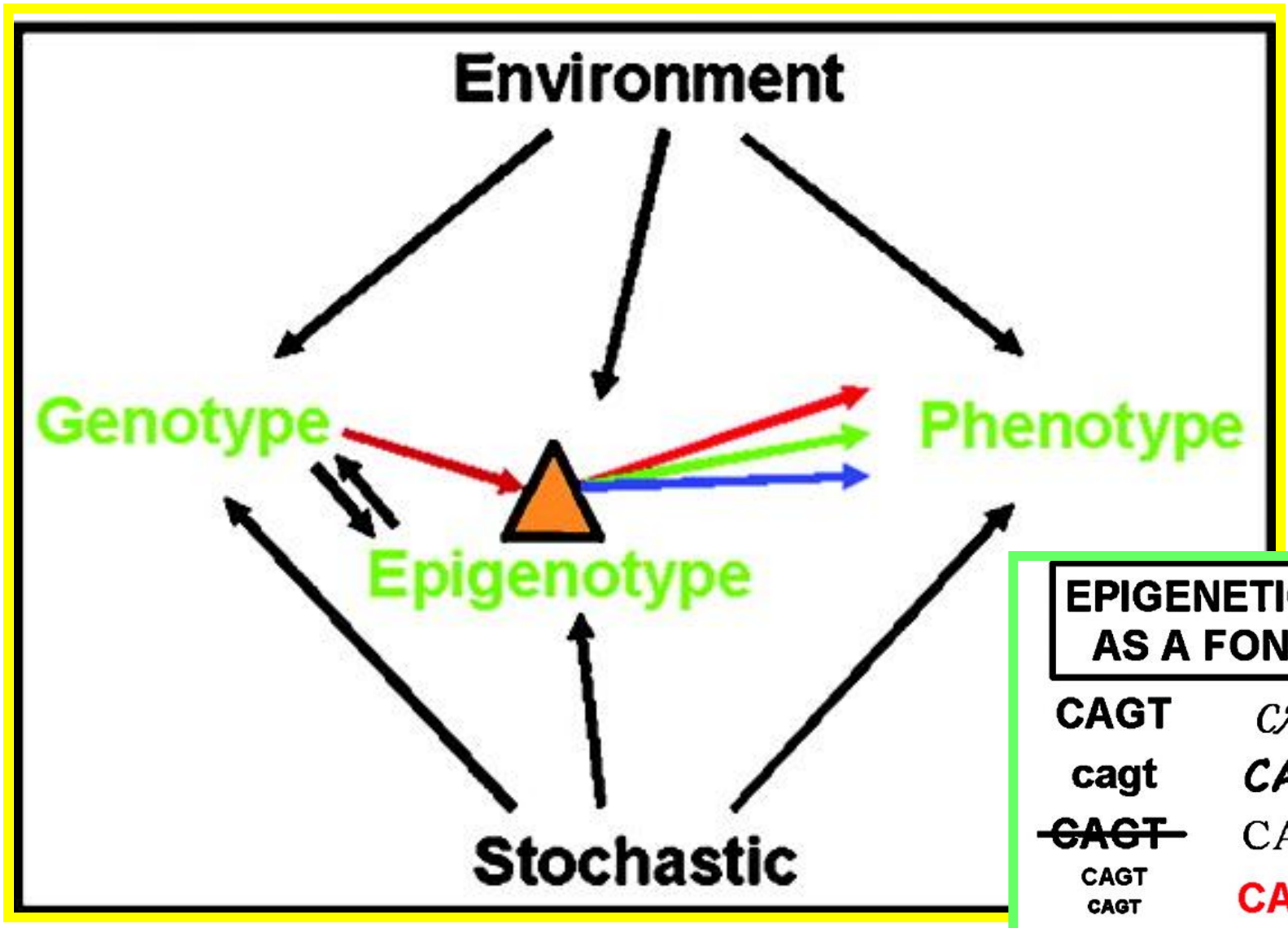
No protein

A number of epigenetic mechanisms are being discovered that control gene expression



Well, that clears it up!

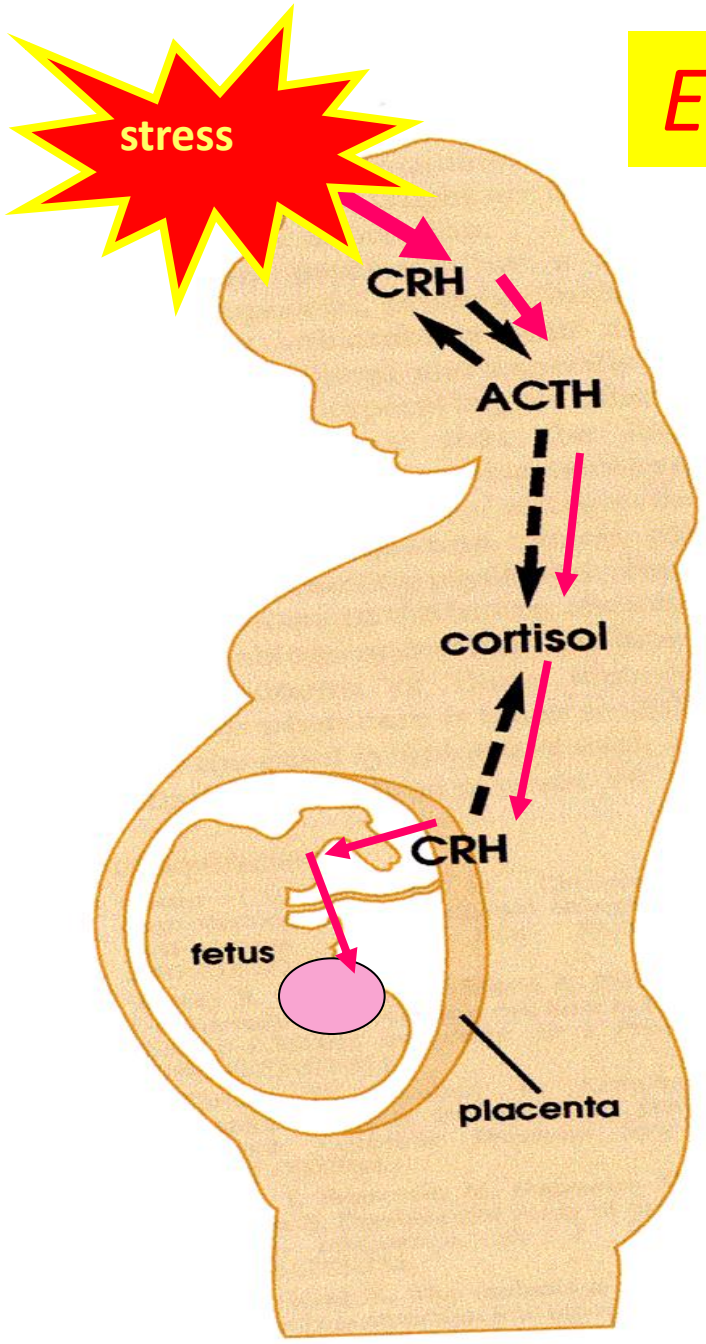
Epigenetic code



EPIGENETICS AS A FONT

CAGT	CAGT
cagt	CAGT
~~CAGT~~	CAGT
CAGT CAGT	CAGT
CAGT	CAGT

Epigenetic Influences



Fetal Programming by Prenatal Stress

The fetus does not develop from a blueprint of its DNA

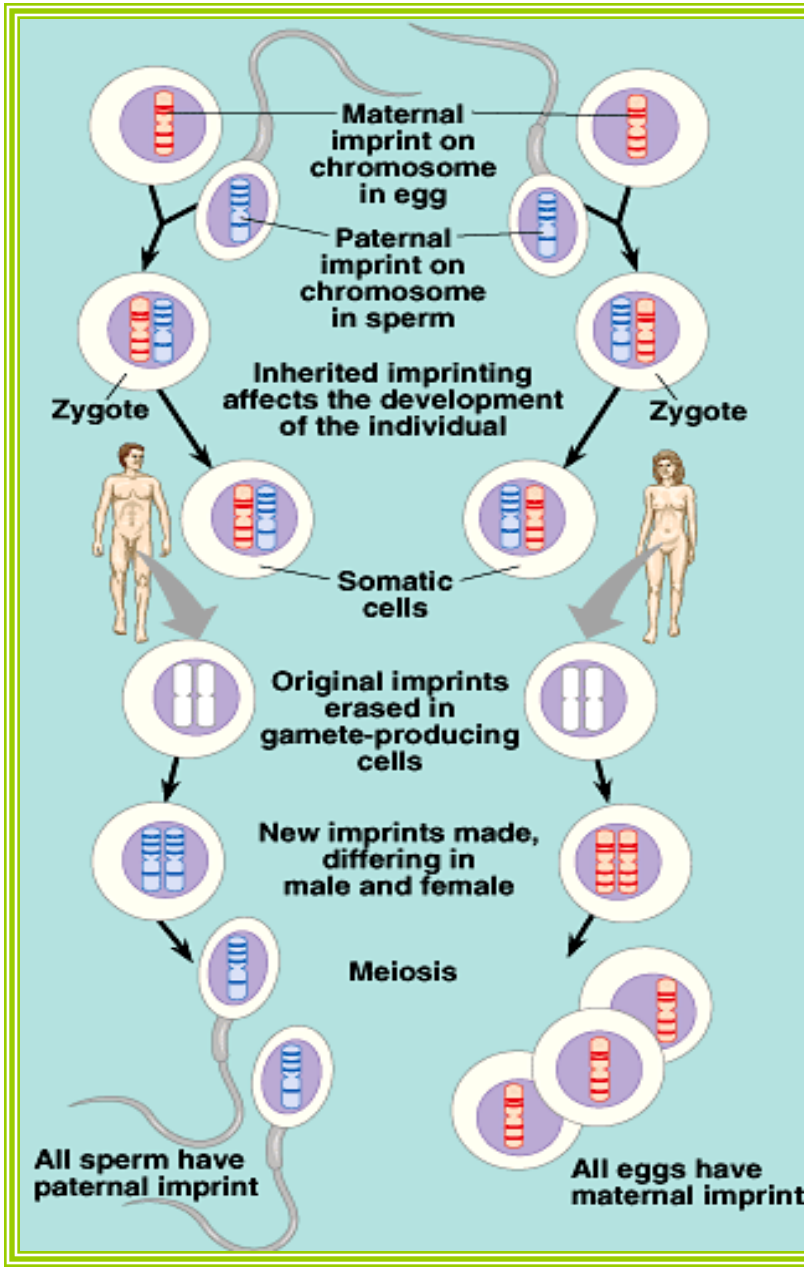
Genomic Imprinting: Epigenetics

The expression of imprinted genes is based on the sex of the parent of origin

Maternal and paternal genomes are not functionally equivalent; both required for development.

Imprinted genes are differentially silenced in the germ cells based on parental sex.

Paternal alleles essential for extraembryonic tissues and for fetal growth and behavior.



Genomic imprinting

Maternal alleles:

Many curb fetal growth, thereby permitting maternal health and resources for multiple offspring. (e.g. *Igf2R, Mash2, Gnas*)

Paternal alleles:

Usually favor offspring growth, daughters social behavior and nurture. The placenta has numerous paternally expressed genes (e.g. *Igf2, Peg3*) that promote fetal growth and nutrient uptake, even to the detriment of mother.

Genomic imprinting

Genetic mechanism for resolving conflict between different parental requirements for reproductive success?

The exception that proves the rule:

Liger - cross breeding a female Tiger to a male Lion.

Tigon - cross breeding a female Lion to a male Tiger.

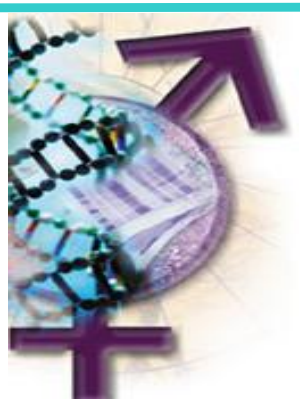
The Life Long Plastic Brain

Parent's Germ Cells

Fetal Programming
Prenatal Exposures

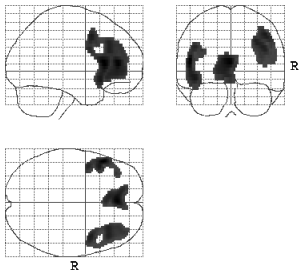
Risk effects of trauma,
substance abuse, injury…
Protective effects of nurture, education,

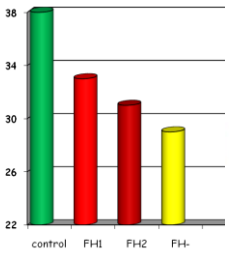
Parents germ cells **fetal Development** **Childhood** **Adolescence** **Adulthood**



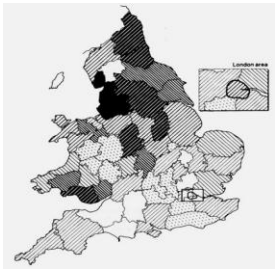
Translational Psychiatry

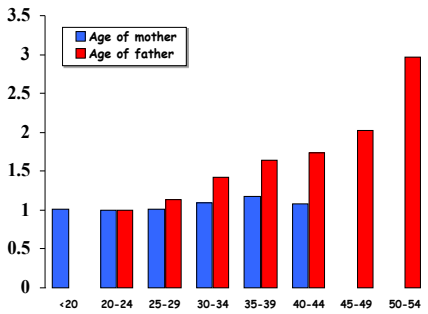
Clinical Research



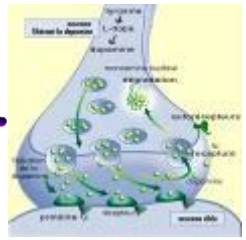


Epidemiology





Human Genetics
Animal Models



“It Seems the Fertility Clock Ticks for Men, Too”

The New York Times

February 27, 2007

Social and Psychiatric Initiatives

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