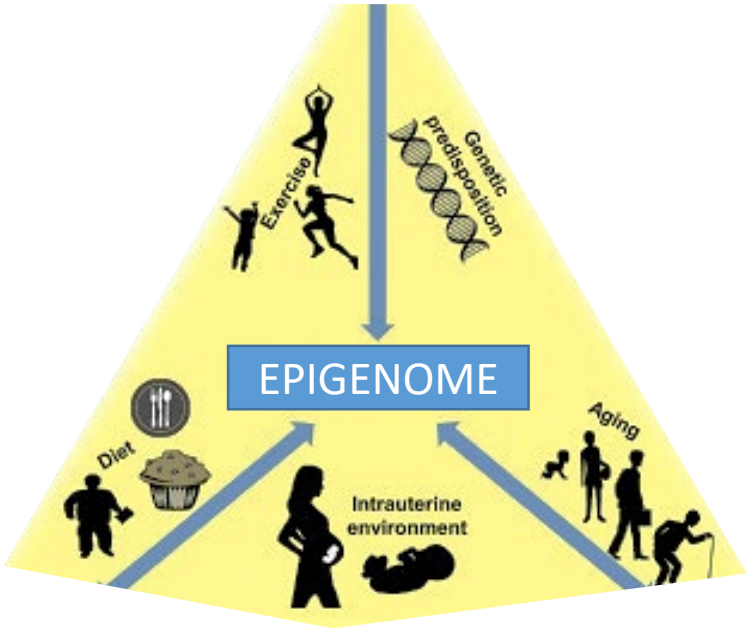
Epigenetics: how sex and gender get under the skin



modified from Ling & Rönn, Cell Metabolism 2019

Edwin Mariman
Professor of Functional Genetics
Maastricht University

TO BE ADDRESSED:

A. DEFINITIONS
B. A CLASSICAL EXAMPLE OF EPIGENETICS
C. MOLECULAR MECHANISM
D. EPIGENETICS, BRAIN AND BEHAVIOR
E. POPULATION (EPI)GENETICS
F. TRANSGENERATIONAL EPIGENETICS

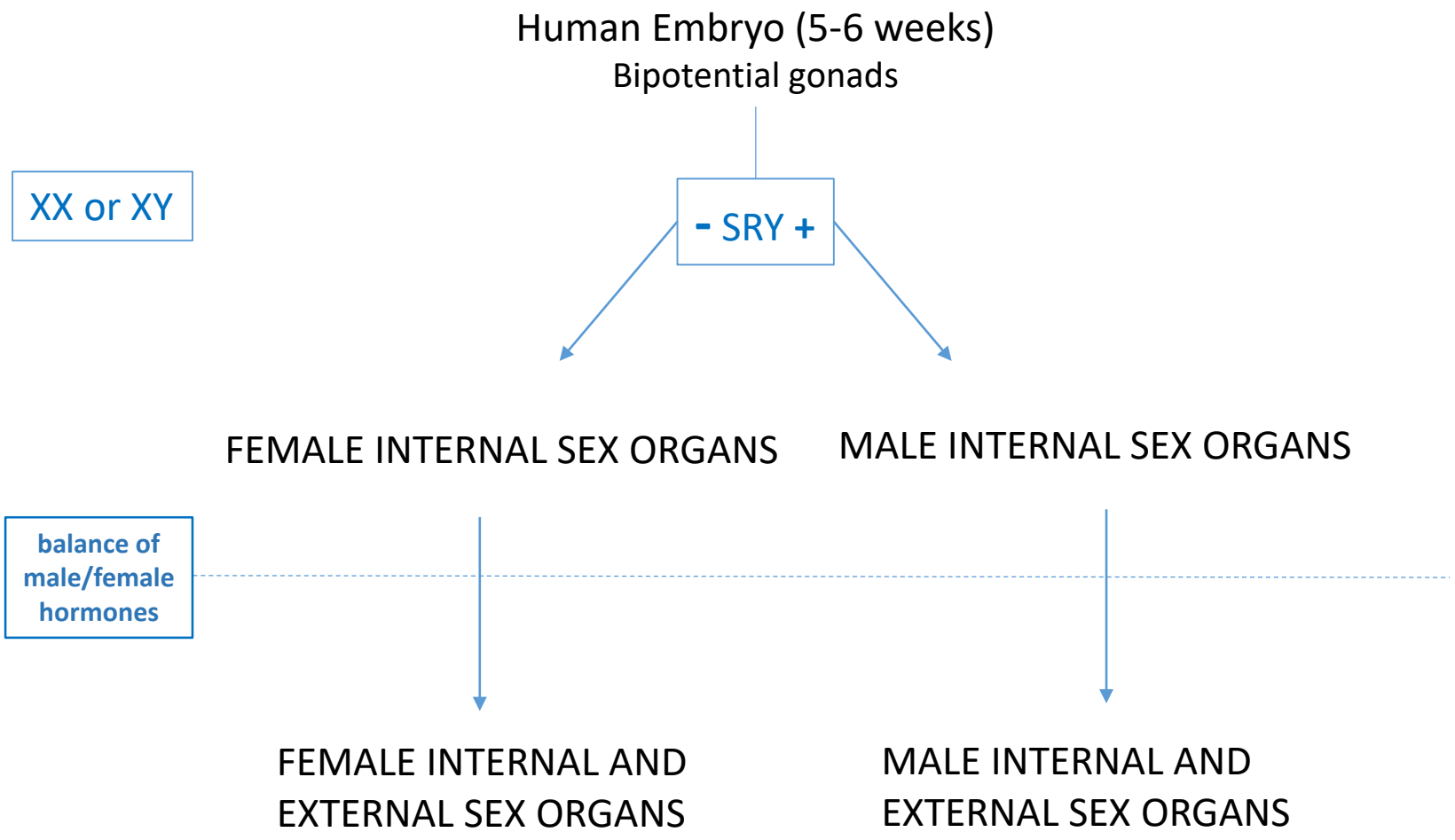
A

DEFINITIONS:

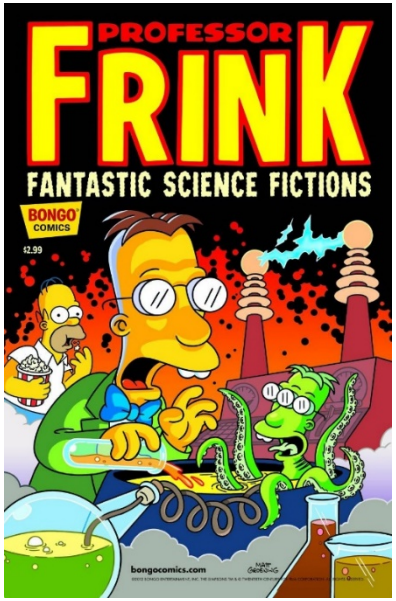
- **SEX DIFFERENCES***
- **GENDER DIFFERENCES***
- **EPIGENETICS**

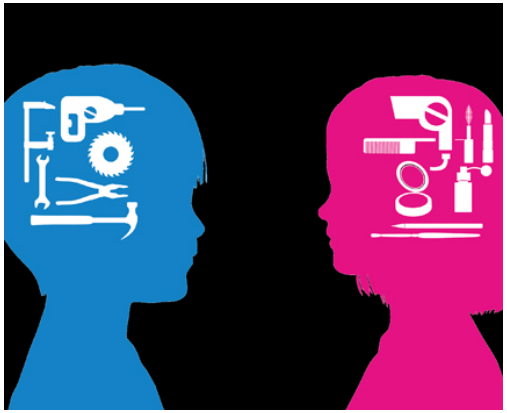
* **Does Gender Leave an Epigenetic Imprint on the Brain?**
Cortes et al., *Frontiers in Neuroscience* 2019

Sex differences are related to sex-chromosomes or gonadal hormones



Gender differences are due to social factors; individuals are treated differently by conspecifics due to the individual's perceived sex.





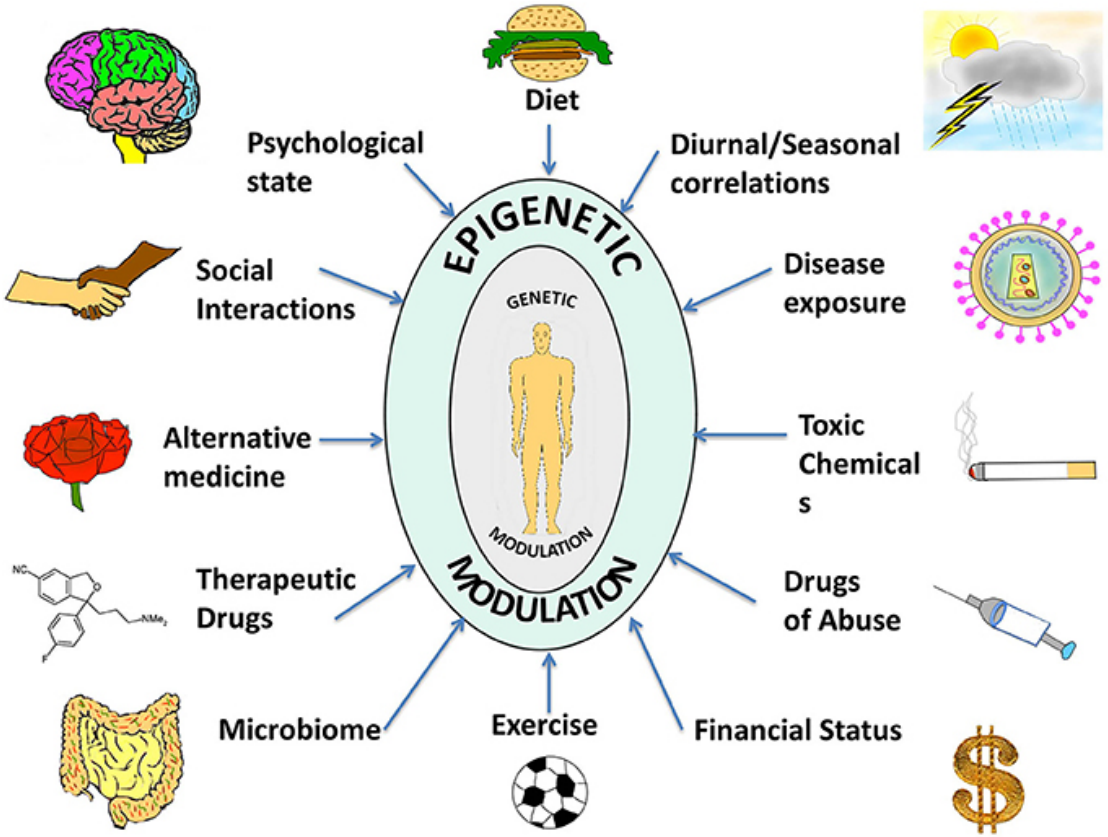
healthmagazine.ae

All of us participate in gender role stereotyping to some degree.

Do you automatically buy your son a car or truck for his birthday or head straight to the Barbie section of your local toy store when you need to buy a gift for your niece?

EPIGENETICS:

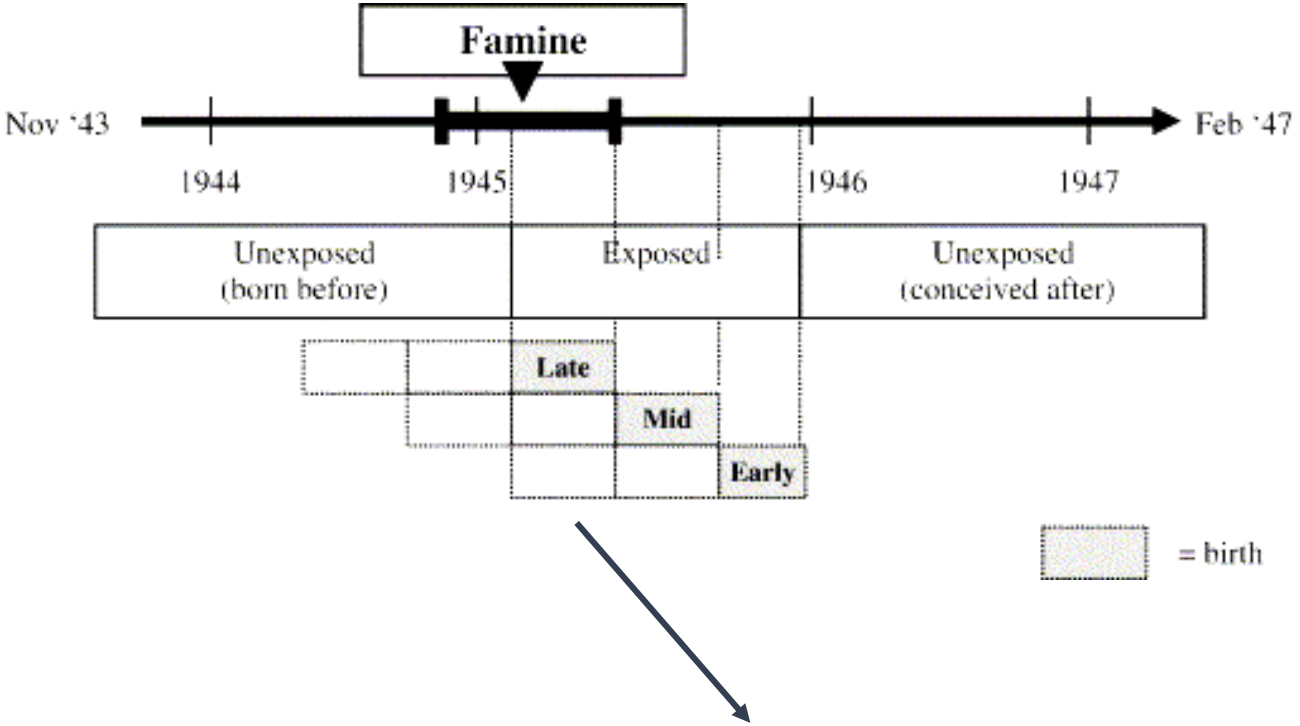
Modulation of the phenotype of an organism by social/environmental influences on gene expression without altering the DNA nucleotide sequence



Kanherkar et al., Frontiers Cell Dev Biol 2014

EXAMPLE SHOWING THE ACTION OF EPIGENETICS:

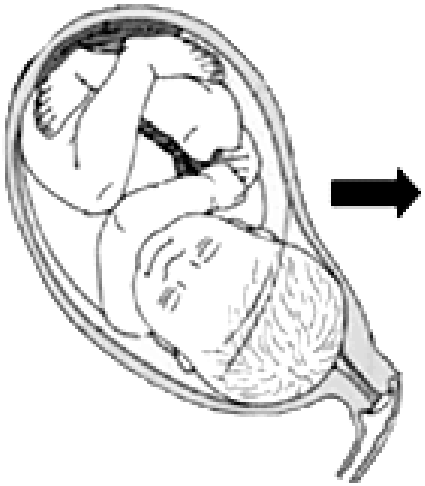
THE DUTCH HUNGER WINTER



In **early** gestation
Glucose intolerance
Atherogenic lipid profile
Altered blood coagulation
Obesity (women only)
Stress sensitivity
Coronary heart disease
Breast cancer

FETAL ORIGINS HYPOTHESIS (DAVID BARKER 1995)

LIMITED FOOD AVAILABILITY



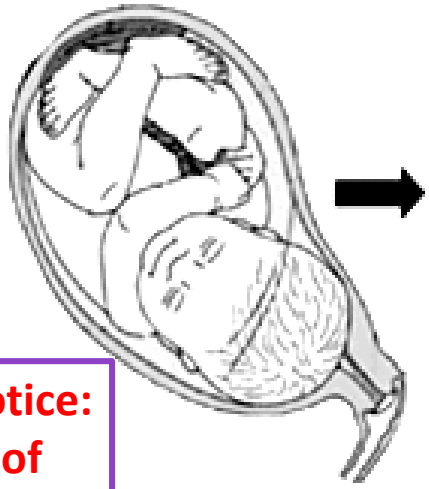
ECONOMIC METABOLISM
'THRIFTY GENOME'

CATCH-UP GROWTH
DURING FIRST YEAR

OBESITY AND
RELATED DISORDERS
(CVD) AT LATER AGE

FETAL ORIGINS HYPOTHESIS (DAVID BARKER 1995)

LIMITED FOOD AVAILABILITY



ECONOMIC METABOLISM
'THRIFTY GENOME'

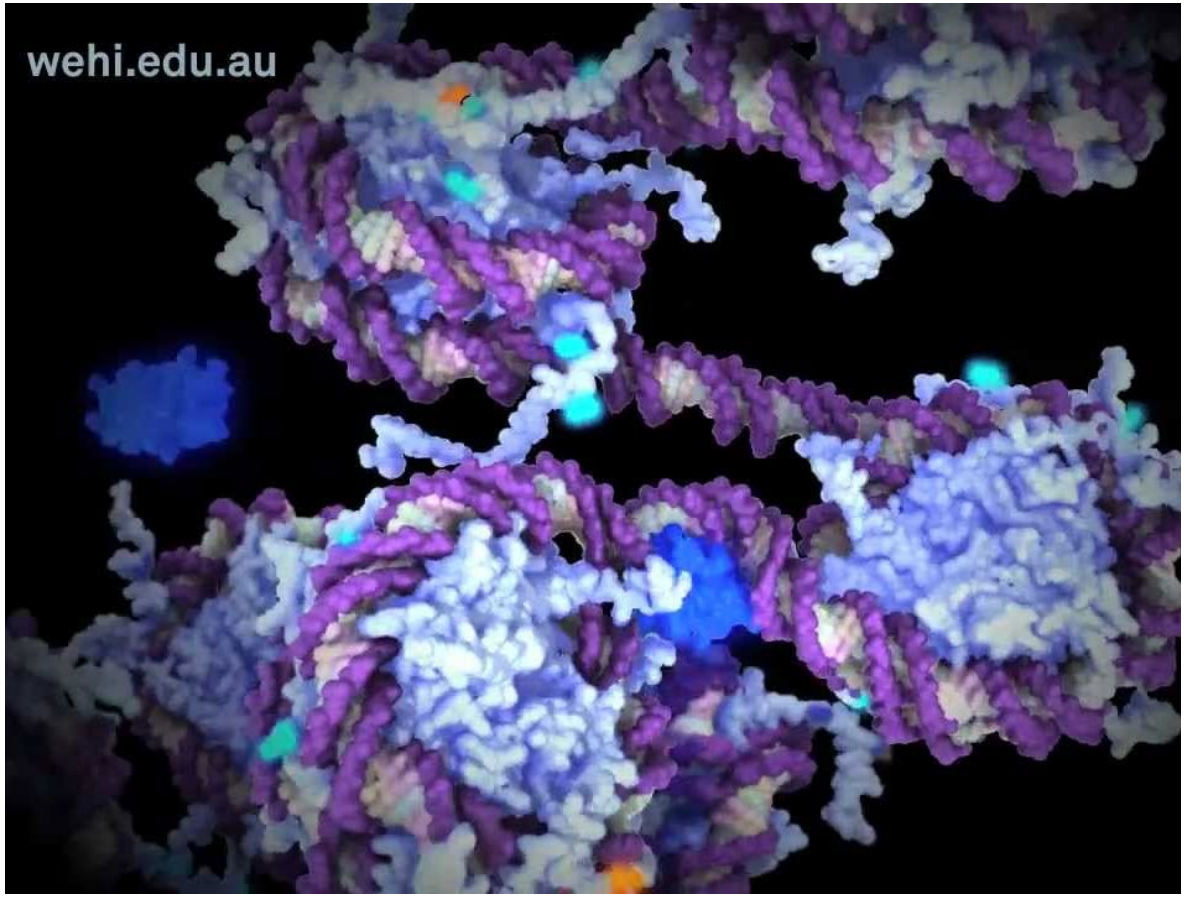
Important Notice: the resetting of gene activity can become fixed

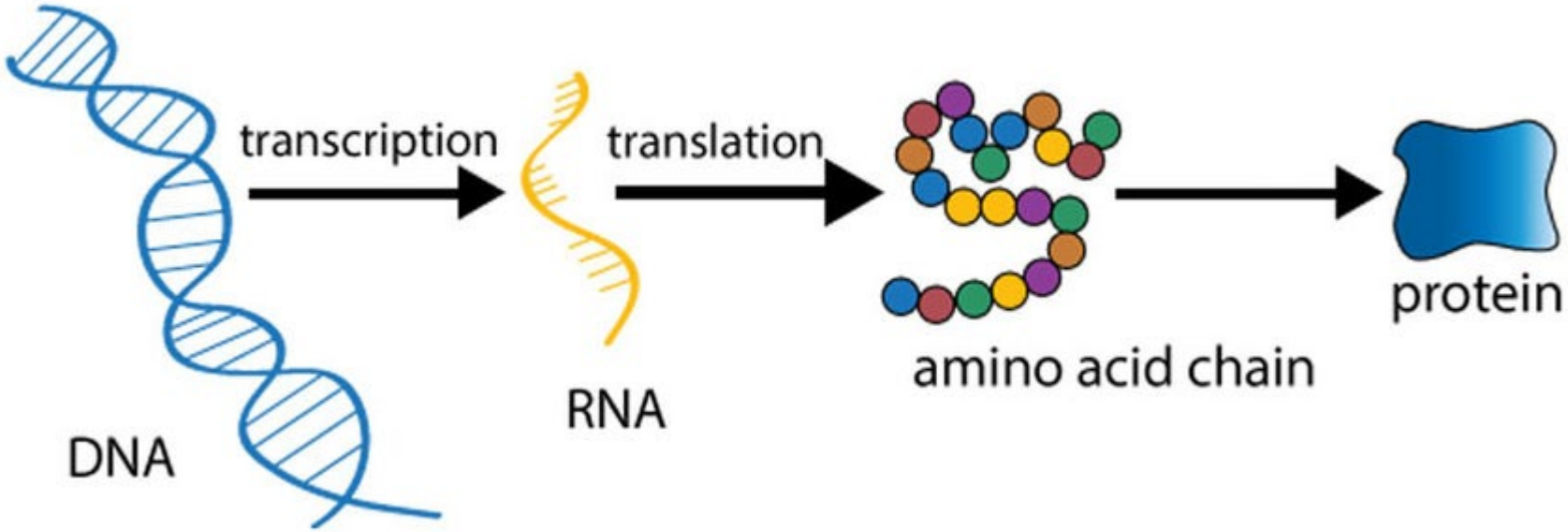
CATCH-UP GROWTH DURING FIRST YEAR

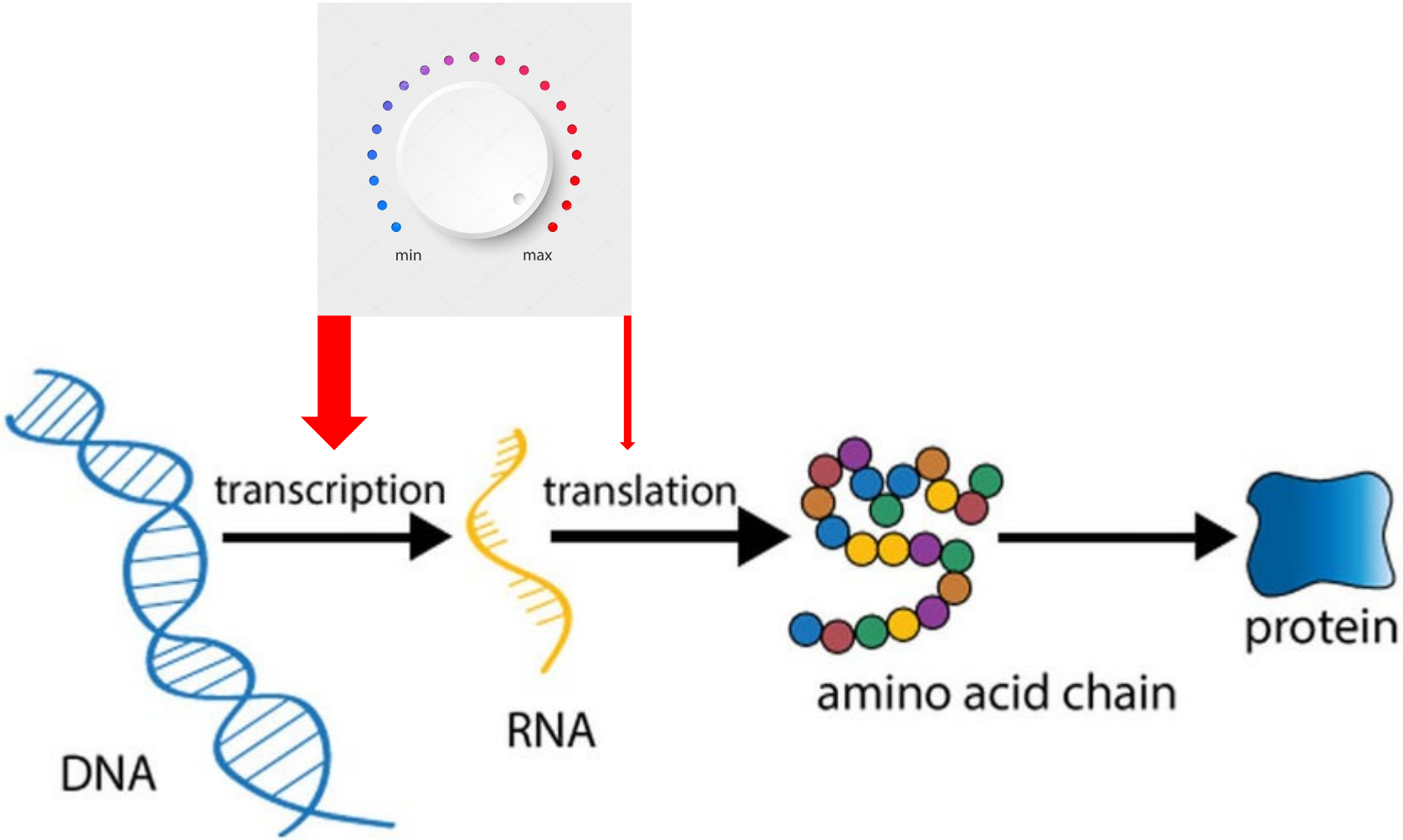
OBESITY AND RELATED DISORDERS (CVD) AT LATER AGE

C

ON THE MOLECULAR MECHANISM OF EPIGENETICS




transcription
translation
DNA
RNA
amino acid chain
protein

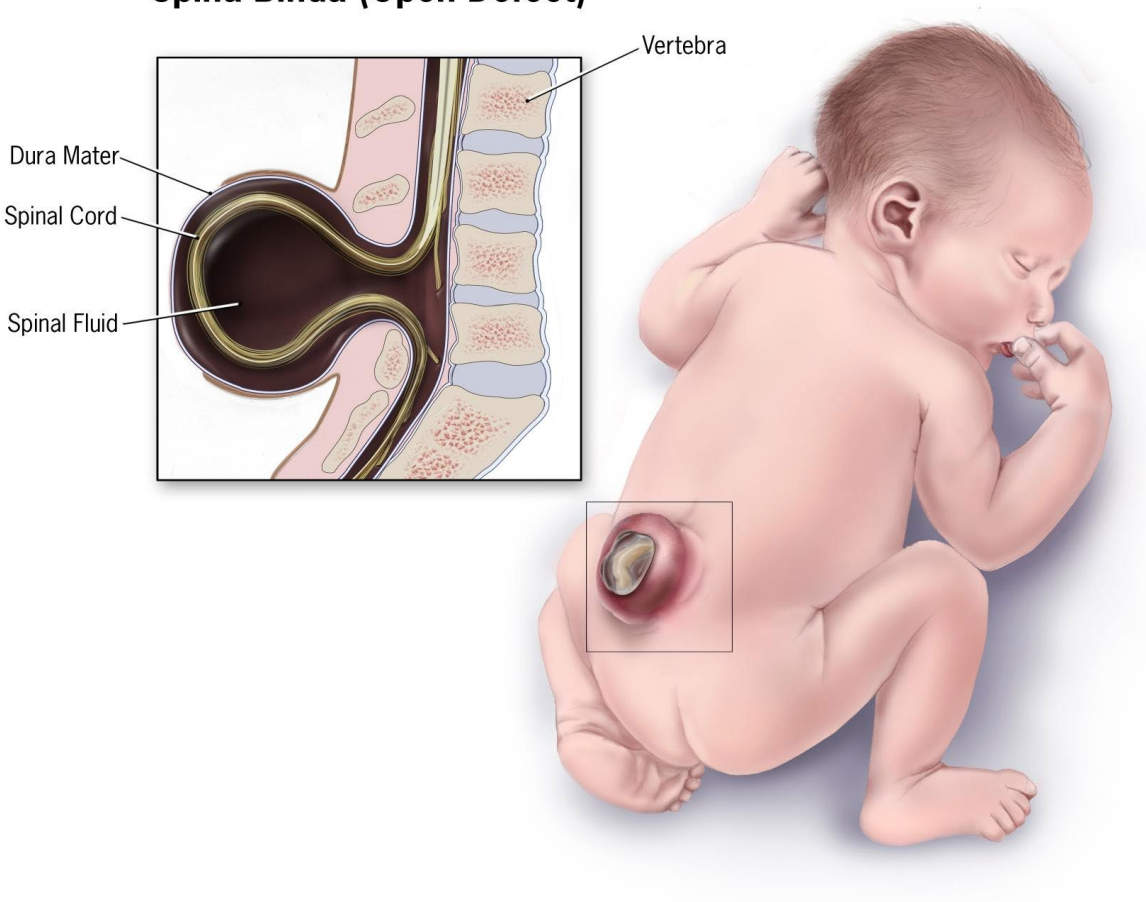

min
max
transcription
translation
DNA
RNA
amino acid chain
protein

One thing that learned us more about
the molecular mechanism of epigenetics:

EFFECT OF THE SEX OF THE PARENT-OF-ORIGIN ON GENE EXPRESSION

NEURAL TUBE DEFECTS

Spina Bifida (Open Defect)

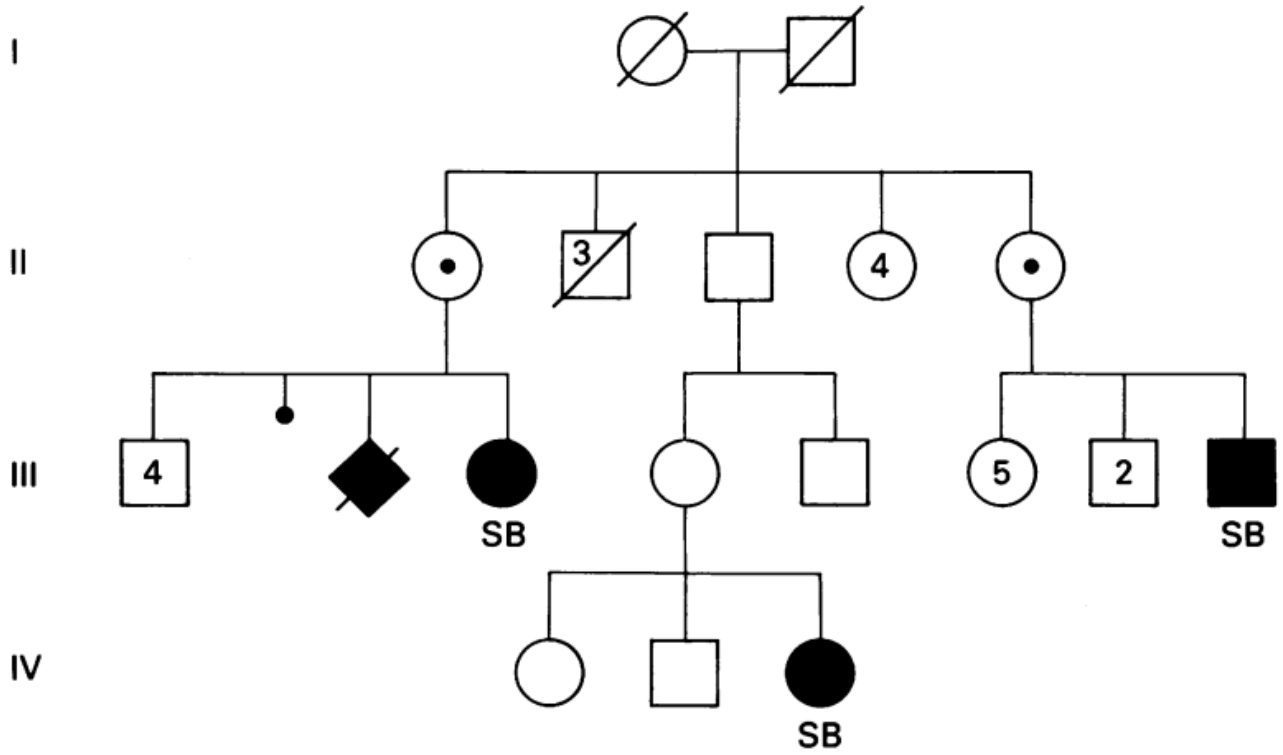


Anencephaly

Illustrations from wikipedia

SEX RATIOS OF AFFECTED AND TRANSMITTING MEMBERS OF MULTIPLE CASE FAMILIES WITH NEURAL TUBE DEFECTS

Mariman ECM & Hamel BCJ. *J. Med. Genet* 1992.

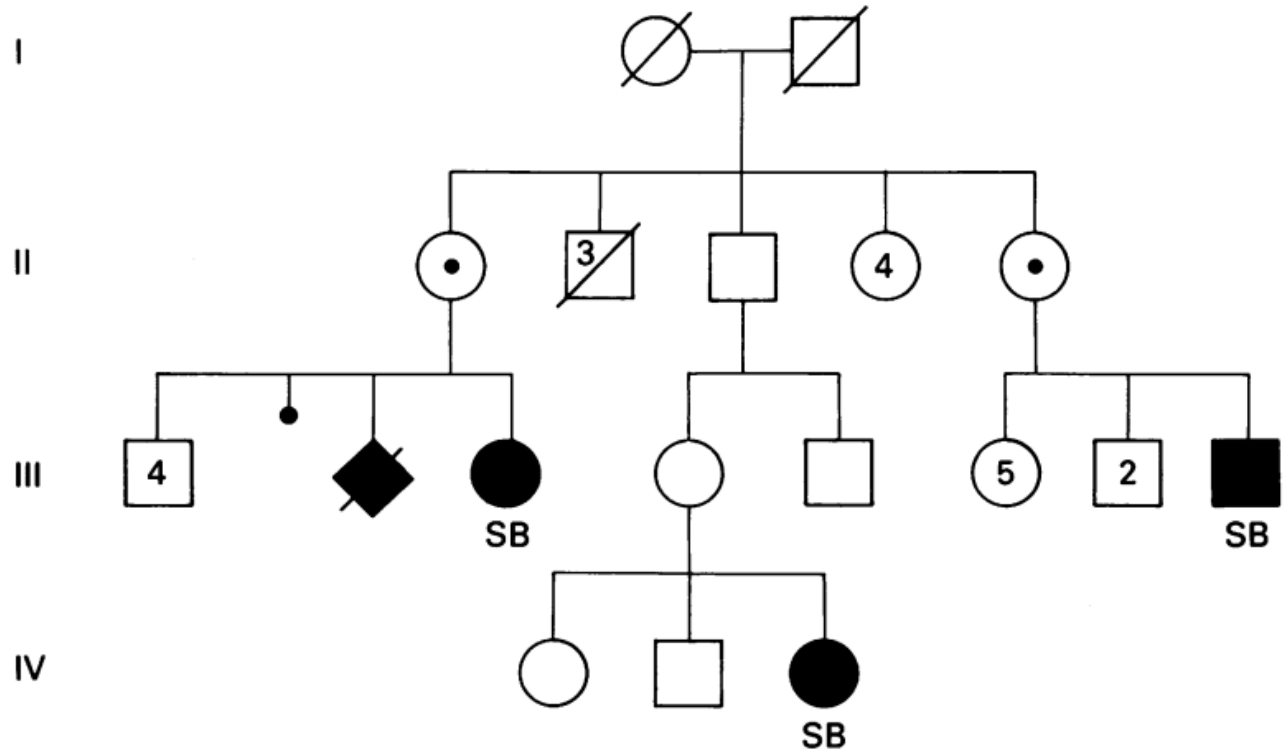


Clinical Genetics Center
Radboud UMC, Nijmegen

Table 3 Determination of the male/female ratio among affected persons and normal transmitters in multiple case families with either NTD or cleft lip ± palate.

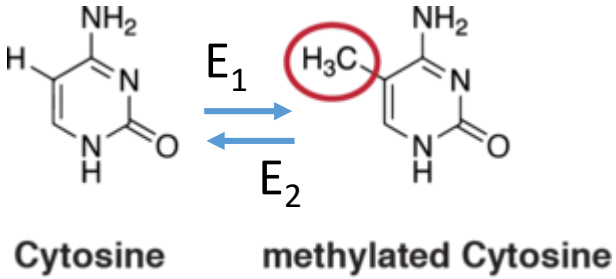
Type of defect		Total	NR*	Male	Female	M/F
Neural tube defects	Affected persons	265	50	113	102	1·1
	Normal transmitters	127	0	51	76	0·7
Cleft lip ± palate	Affected persons	97	4	58	37	1·6
	Normal transmitters	39	1	25	13	1·8

* NR = sex not recorded.

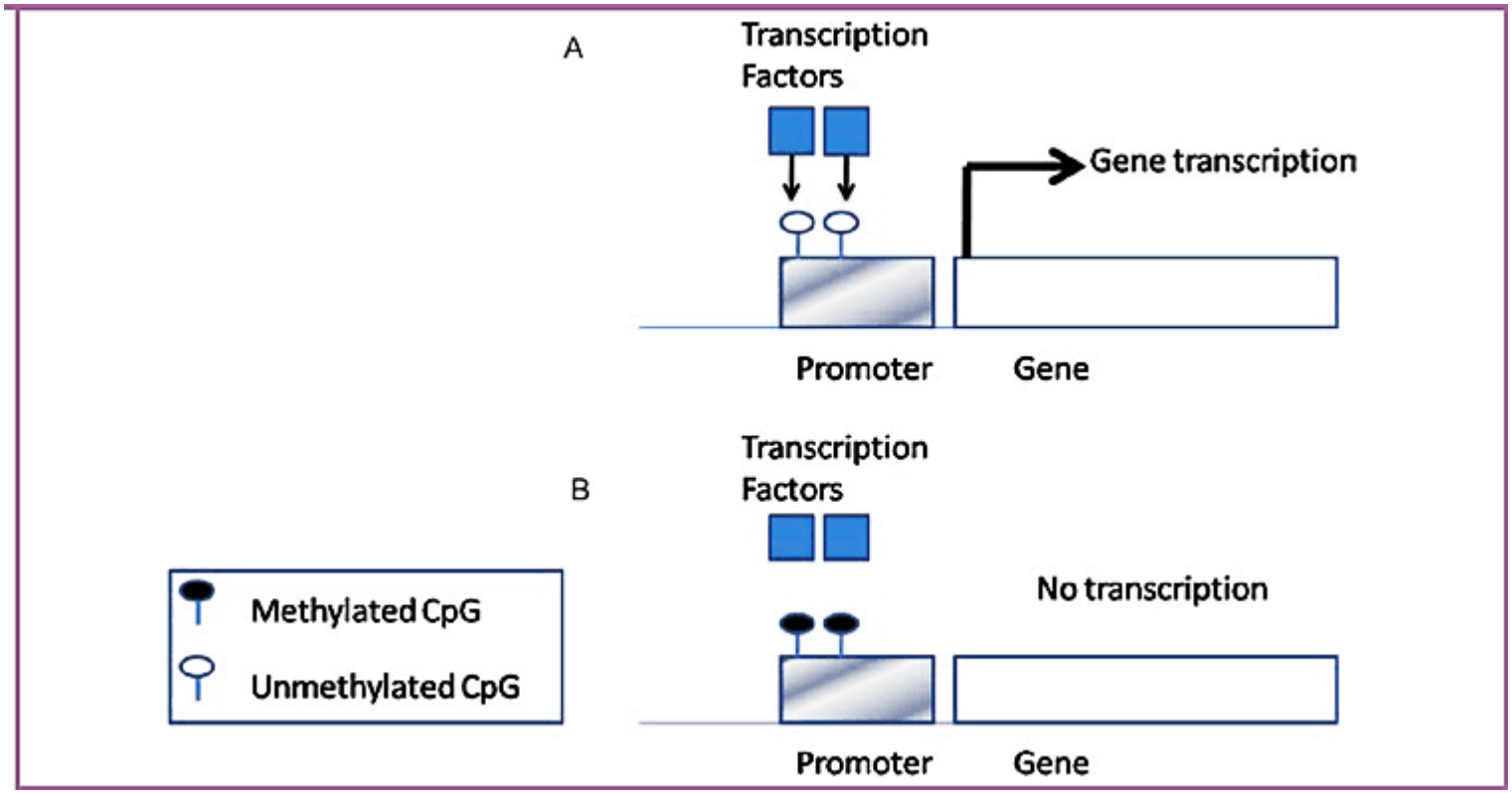


DNA METHYLATION

- - - C - G - - -
- - - G - C - - -

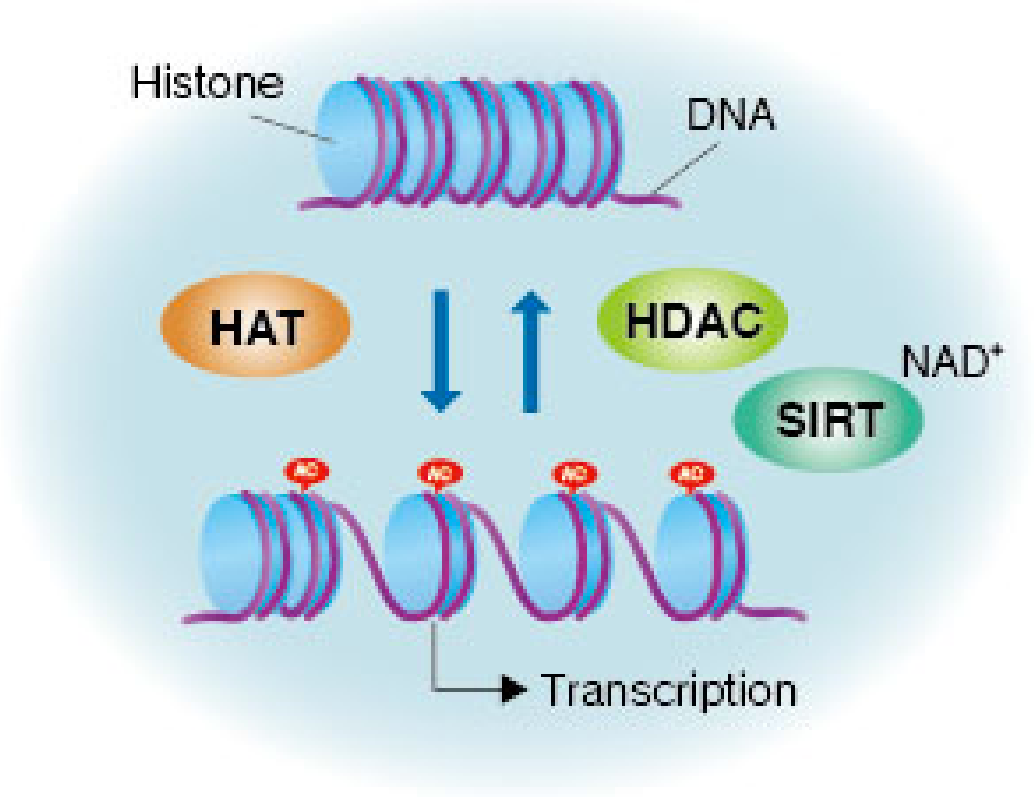


wikipedia



from Lim et al., The Obstetrician and Gynaecologist 2010

HISTON MODIFICATION



MBL Lifescience

SUMMARY SO FAR:

- EXTERNAL INFLUENCES LEAD TO A STRESS SITUATION
- THIS INDUCES ADJUSTMENT OF GENE ACTIVITY
- BY DNA METHYLATION OR HISTON MODIFICATION
- RESETTING OF GENE ACTIVITY CAN REMAIN FIXED AT LATER LIFE

D

EPIGENETICS, BRAIN AND BEHAVIOR

CAN MENTAL STRESS AT EARLY AGE LEAD TO EPIGENETIC CHANGES?

SEXUAL DIFFERENTIATION OF THE BRAIN

GONADAL HORMONES

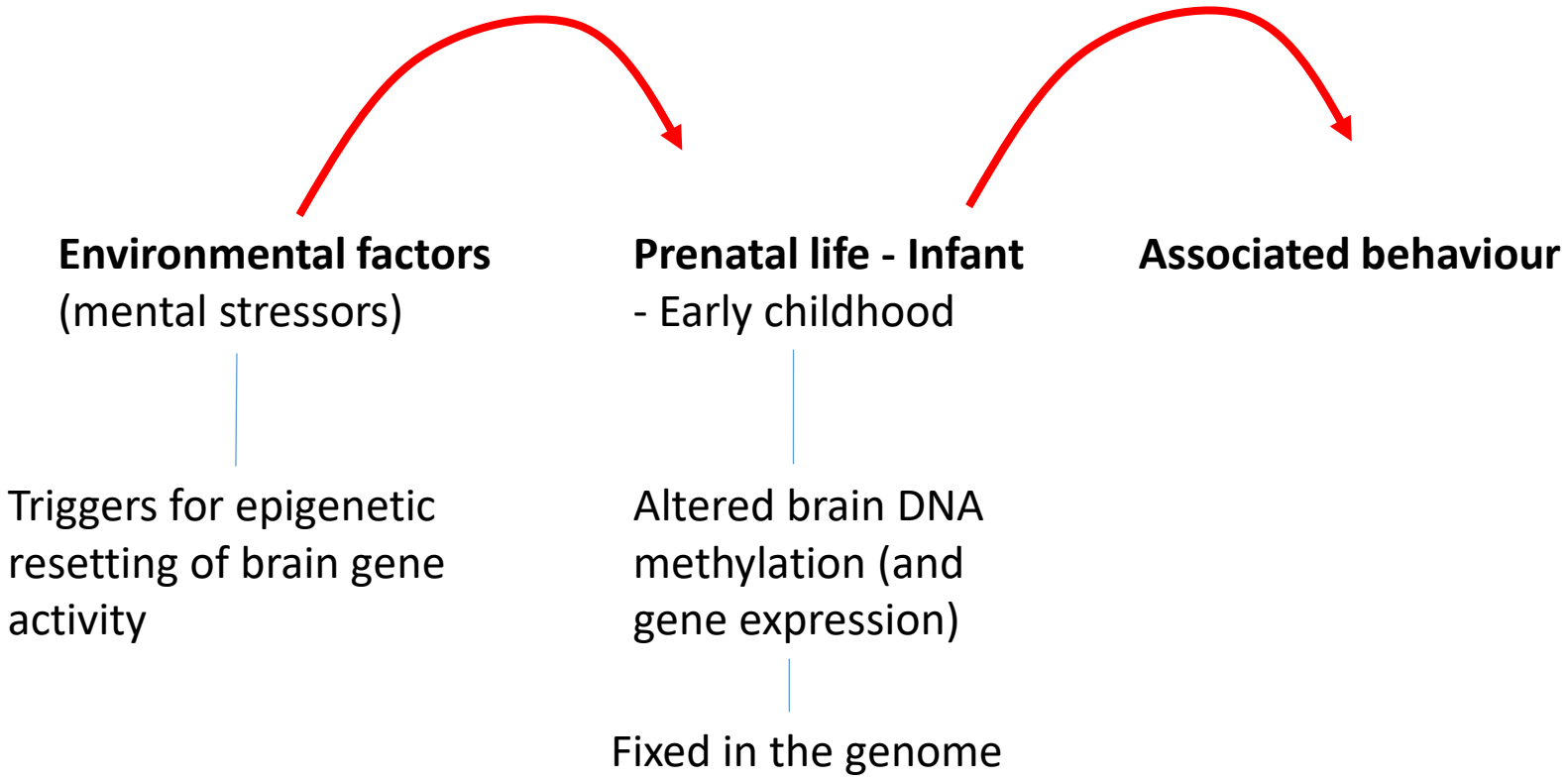
MALE EPIGENETIC IMPRINT

FEMALE EPIGENETIC IMPRINT

Volume 95
Issues 1-2
2017

DIMORPHIC GENE EXPRESSION IN THE BRAIN

CAN MENTAL STRESS AT EARLY AGE LEAD TO EPIGENETIC CHANGES THAT DETERMIN LATER LIFE BEHAVIOR?



Motherly Affection: Nurturing the newborn

MATERNAL ANOGENITAL LICKING IN RATS: EXPLORING THE DAM'S DIFFERENTIAL SEXUAL TREATMENT OF PUPS

Brouhette-Lahlou et al., *Chemical Signals in Vertebrates*, ed. New York 2001

GENDER INFLUENCES: Male pups are licked more than female pups

Male pups have testosteron in urine

↓

Sensed by the mother

↓

Mother licks anogenital part of the male pup

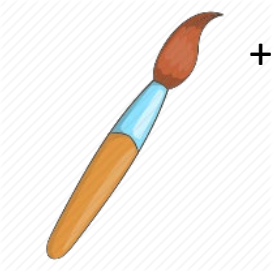
↓

Licking changes the DNA methylation
of the Glucocorticoid Receptor gene
promoter in the brain of the male pup

↓

Stimulation of adult male's reproductive behaviour and performance

Paintbrush experiment



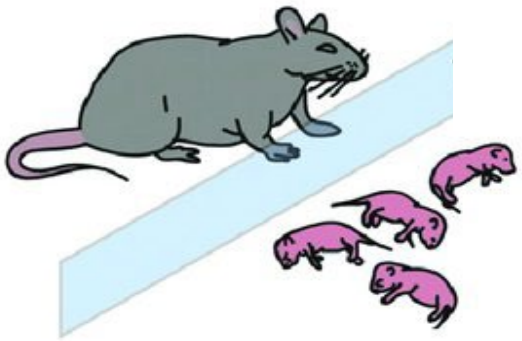
\+ female neonates → masculinisation of the DNA methylation

EARLY LIFE STRESS

Mother-infant separation leads to hypoactive behavior in adolescent Holtzman rats.

Spivey J, et al. Behav Processes. 2008.

Good maternal care



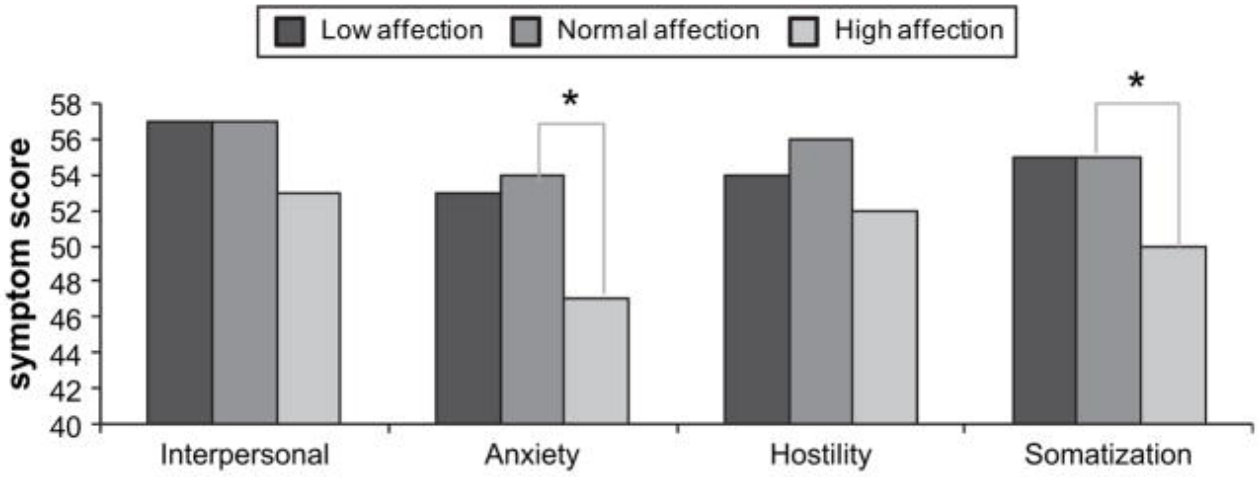
Mother's affection at 8 months predicts emotional distress in adulthood

Maselko et al., J. Epidemiol. Community Health 2011.

The National Colaborative Perinatal Project
The Providence, Rhode Island birth cohort

Infant-mother interaction by observation

Emotional functioning by Symptom Checklist-90
(average age 34, N=482)



*denotes difference is statistically significant at <p0.05

However, influence of reduced maternal affection during 8 months – 34 years cannot be excluded

ONE CHILD POLICY IN CHINA

CHILDREN IN ORPHANAGES: FEMALES >> MALES

→ GENDER INLFUENCE DURING DEVELOPMENT

SUMMARY:

ENVIRONMENTAL/SOCIAL INFLUENCES	(food availability, early life stress)
CAN CHANGE THE EPIGENETIC MARKINGS	(DNA-methylation)
AND RESET GENE EXPRESSION	(metabolism, brain)
LEADING TO LATER LIFE EFFECTS	(health, (sexual) behavior)

GENDER DIFFERENCES IN ALCOHOL ABUSE

Dr. W.B. Huddleston Slater in the book '*Ja, Ik Wil!*', 1947:

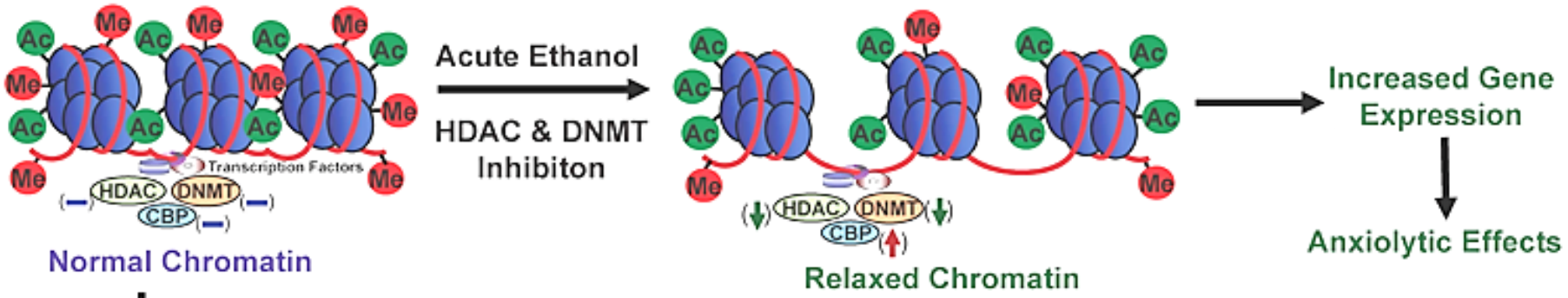
'***A drunk man is ridiculous, a drunk woman is horrific***'

Societal acceptance

More accepted for men than for women (GENDER)

Postmortem: **Alcohol addicts have a different brain DNA methylation profile (correlation)**

Mechanistic: Most research in animals focus on histon modification



from Alcohol Research (NIH): Current Reviews 34 nr.3

ETHANOL

LIVER

ACETATE

BRAIN

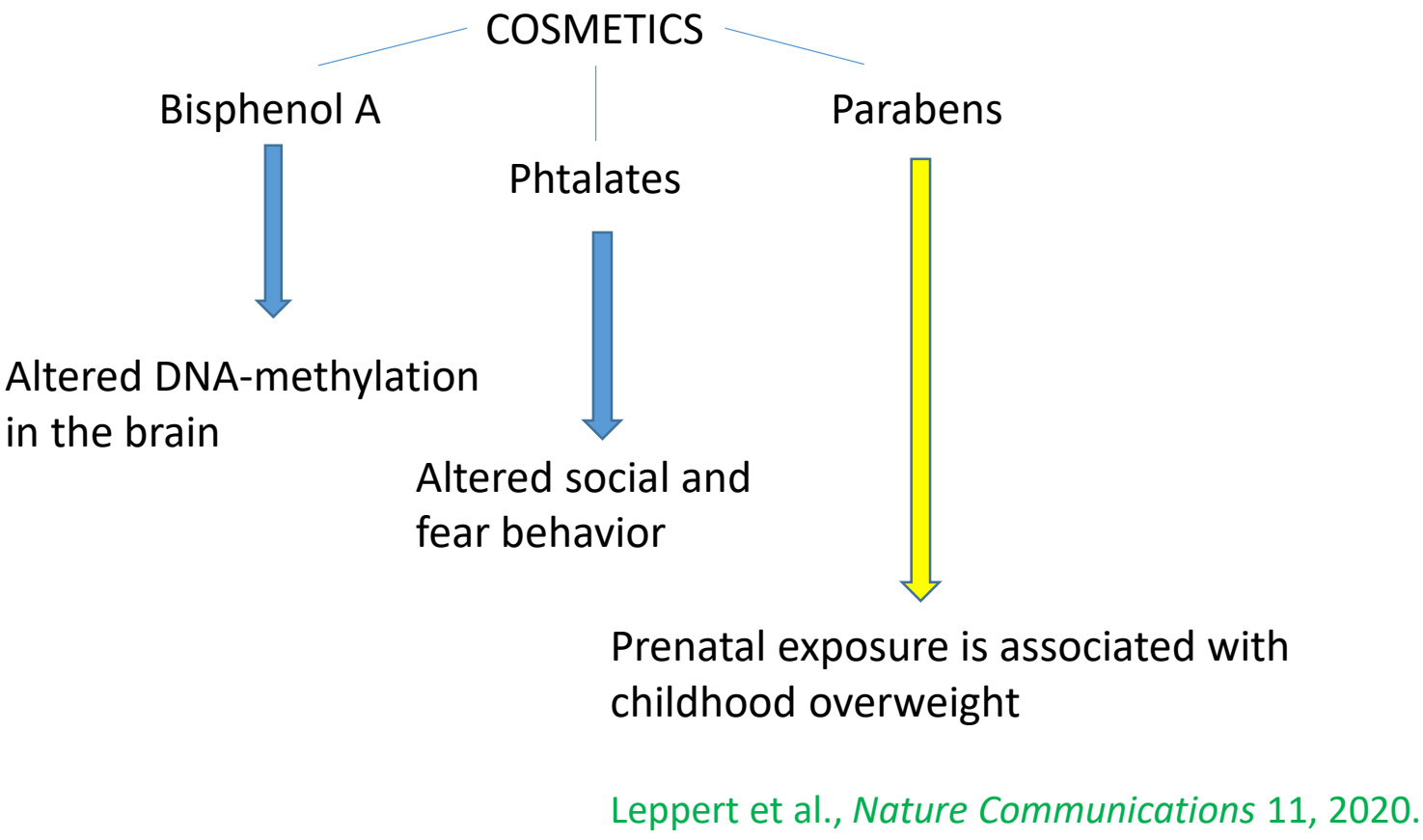
HISTON ACETYLATION

INCREASED EXPRESSION OF CERTAIN GENES IN THE BRAIN

Alcohol metabolism contributes to brain histone acetylation

Mews et al, Nature 574, 2019.

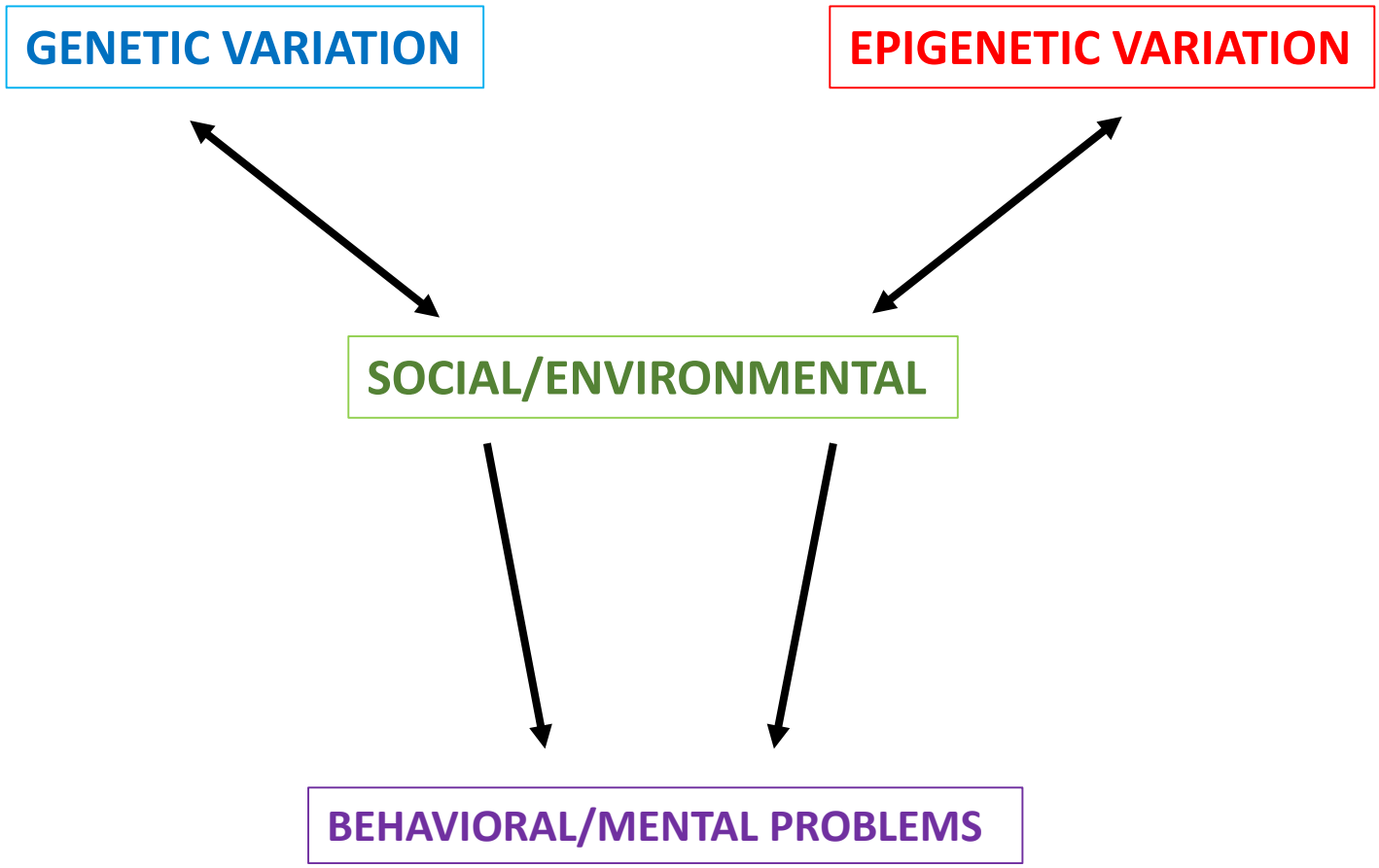
GENDER-BASED EPIGENETIC CHANGES BY USE OF COSMETICS



Leppert et al., *Nature Communications* 11, 2020.

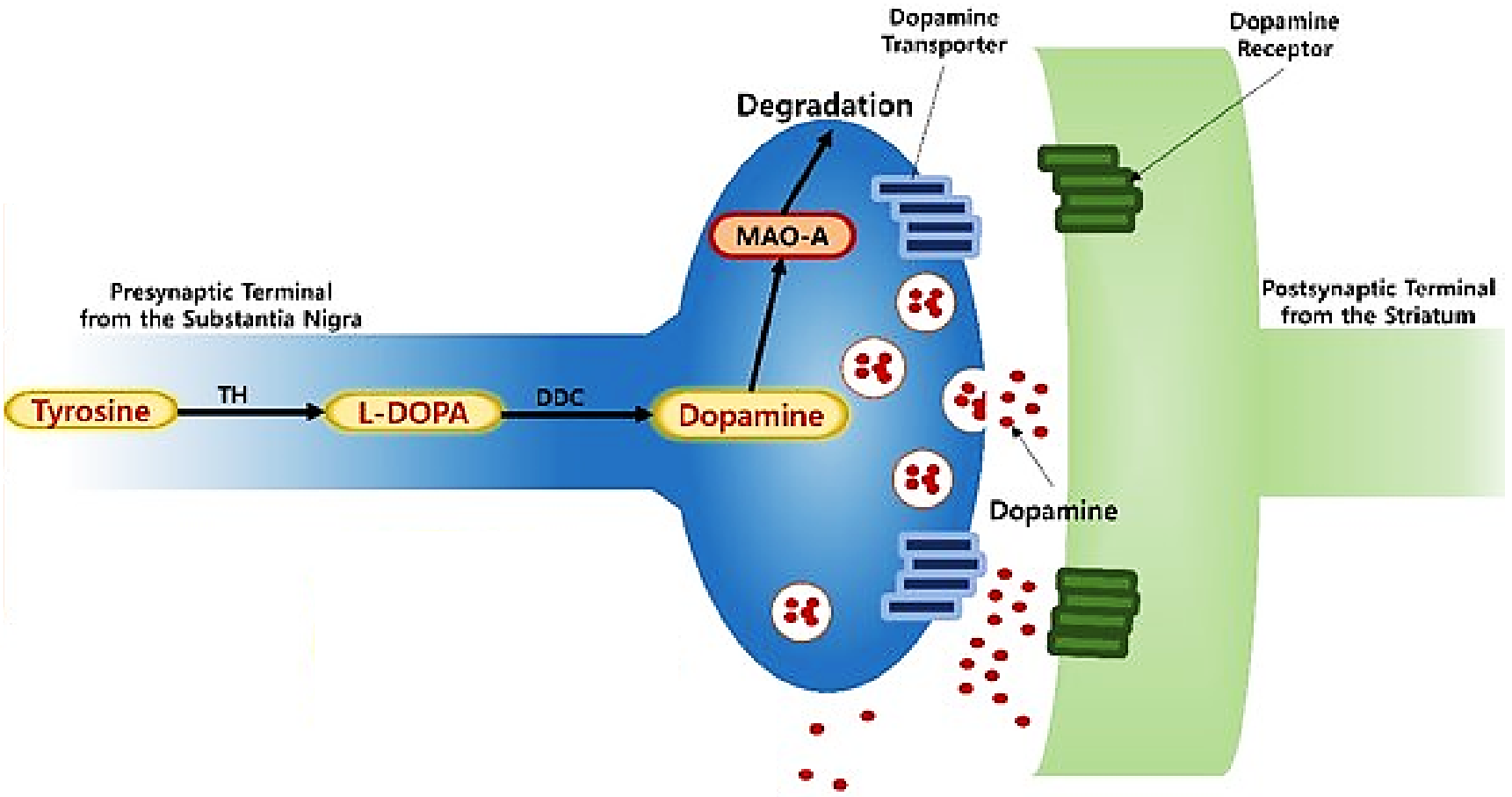
E

POPULATION (EPI)GENETICS



Early life stress ~ MonoAmine Oxidase (MAOA): the connection of genetics and epigenetics

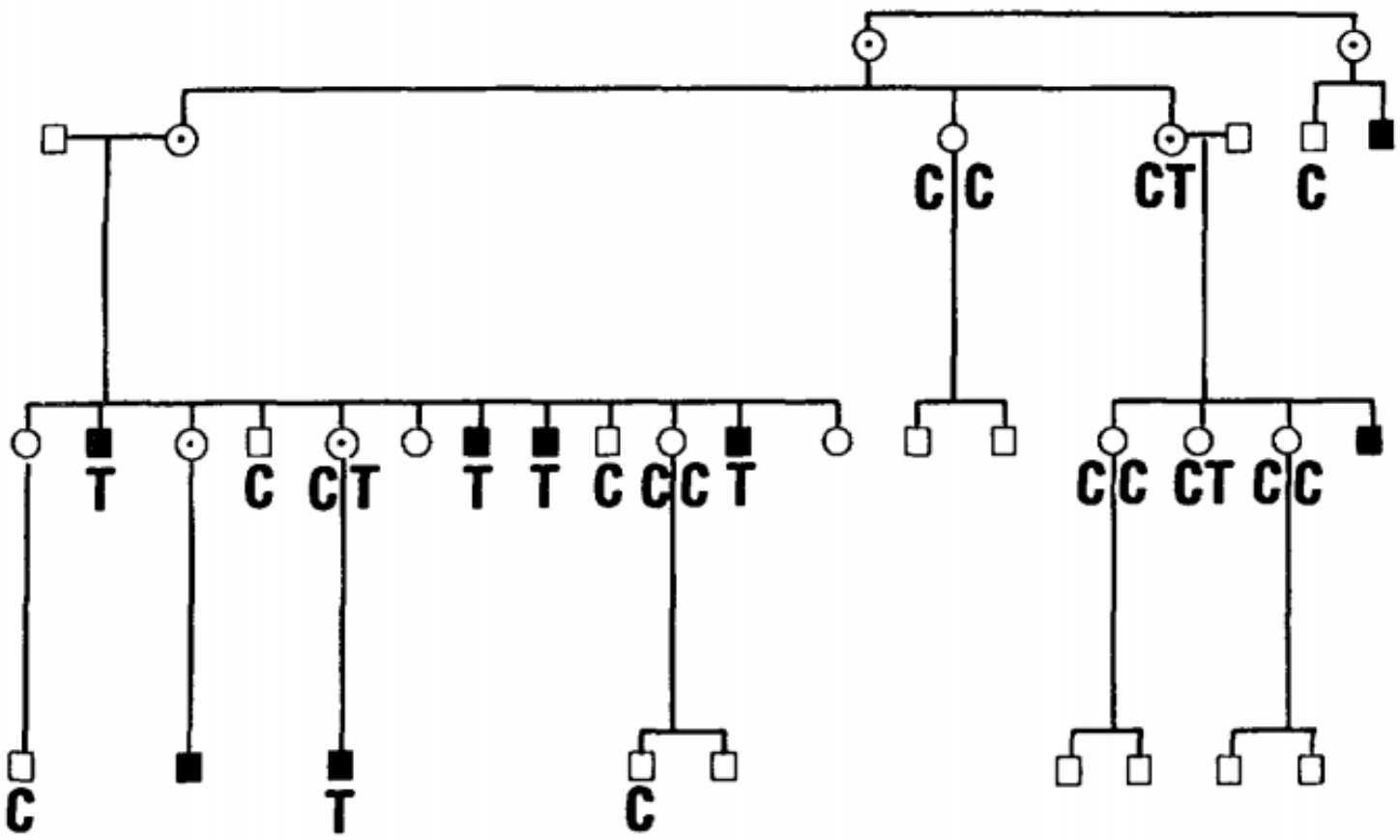
MAOA degrades neurotransmitters (serotonin, dopamin) after re-uptake from the synaptic cleft.



from: Jung et al., Int. J. Mol. Sci. 2019

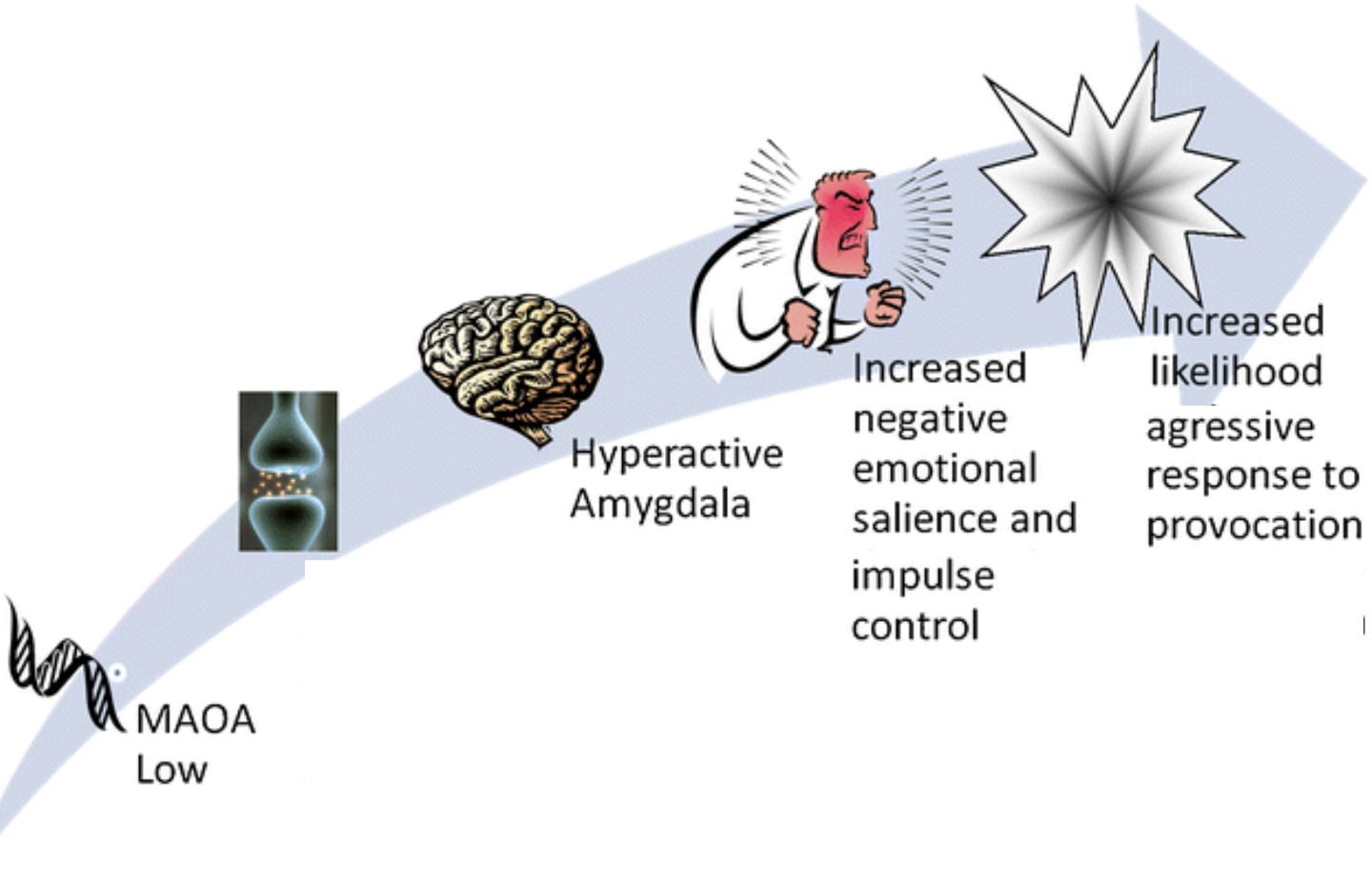
Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A

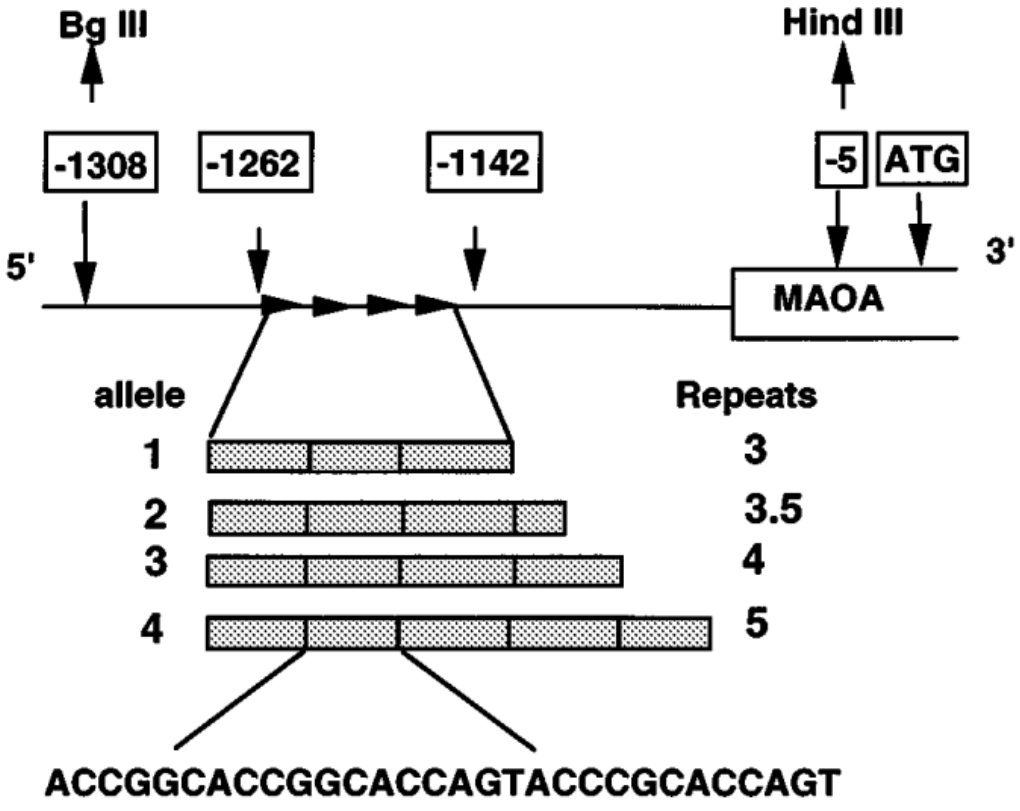
Brunner et al. Science 1993.

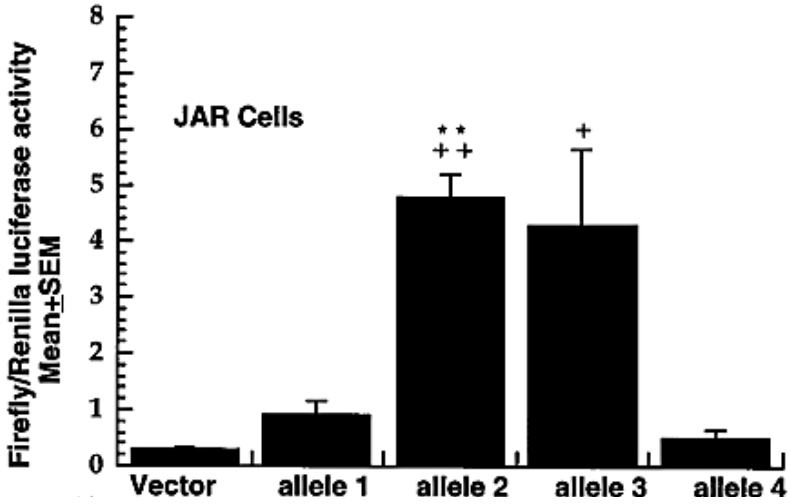


Characteristics of the Brunner Syndrome:

borderline mental retardation and a tendency toward aggressive outbursts, often in response to anger, fear, or frustration. Other types of impulsive behavior that occurred in individual cases included arson, attempted rape, and exhibitionism.

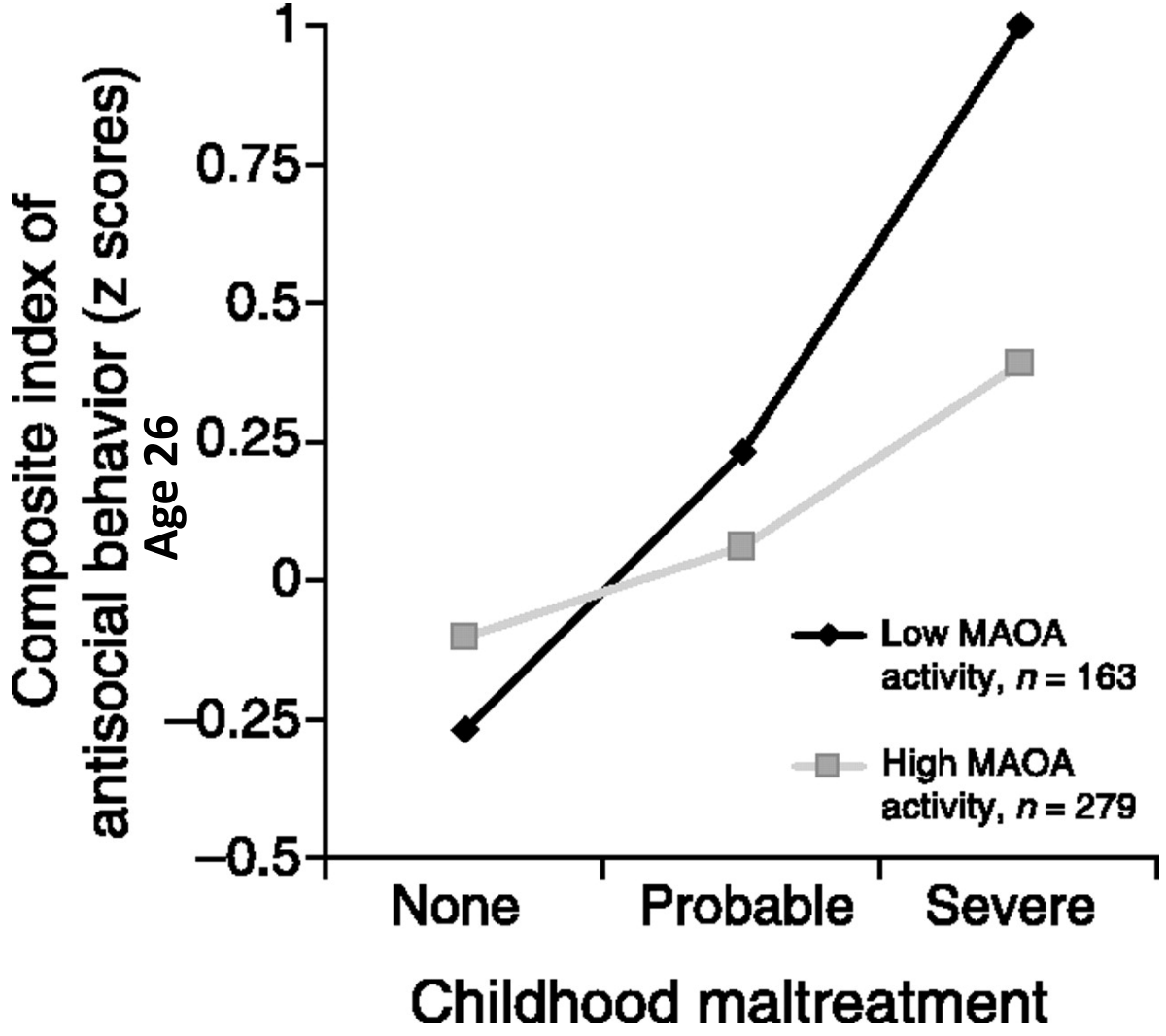



Bg III
Hind III
-1308
-1262
-1142
-5
ATG
5'
3'
MAOA
allele
Repeats
1
3
2
3.5
3
4
4
5
ACCGGCACCGGCACCAGTACCCGCACCAGT


Firefly/Renilla luciferase activity
Mean±SEM
JAR Cells
0
1
2
3
4
5
6
7
8
++
+
Vector
allele 1
allele 2
allele 3
allele 4

Role of Genotype in the Cycle of Violence in Maltreated Children

Caspi et al., Science 2002



Methylation is negatively correlated with MAOA enzymatic activity in healthy men

Associations of monoamine oxidase A gene first exon methylation with sexual abuse and current depression in women.
Checknita et al., J. Neural Transmission 2018.

91 Swedish women with child abuse and 23 non-abused controls. Age: 22 y (SD=4y)

- SA was associated with hypermethylation of the MAOA first exon relative to no-abuse.
- Hypermethylation of MAOA first exon mediated the association of SA with current depression.

Other studies:

- Male offenders with antisocial personality disorder (ASPD) showed **hypermethylation** of this region relative to healthy men
- **Hypomethylation** of this region was observed among women with depression and those with panic disorder relative to healthy women

Two remarks relating to human studies:

- results are associations, not causal information (-> animal studies)

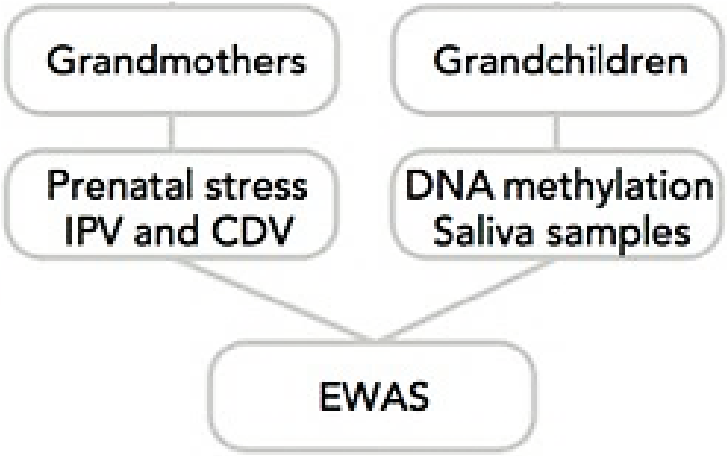
- epigenetic (DNA-methylation) marks are determined in lymphocytes

F

TRANSGENERATIONAL EPIGENETICS

- Are (gender induced) epigenetic changes inherited?

Grandmaternal stress during pregnancy and DNA methylation of the third generation: an epigenome-wide association study.
Serpeloni et al., Translational Psychiatry 2017.



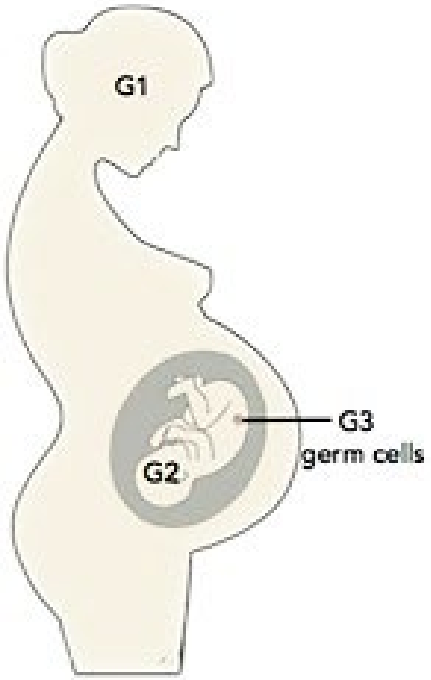
155,000 CpG sites

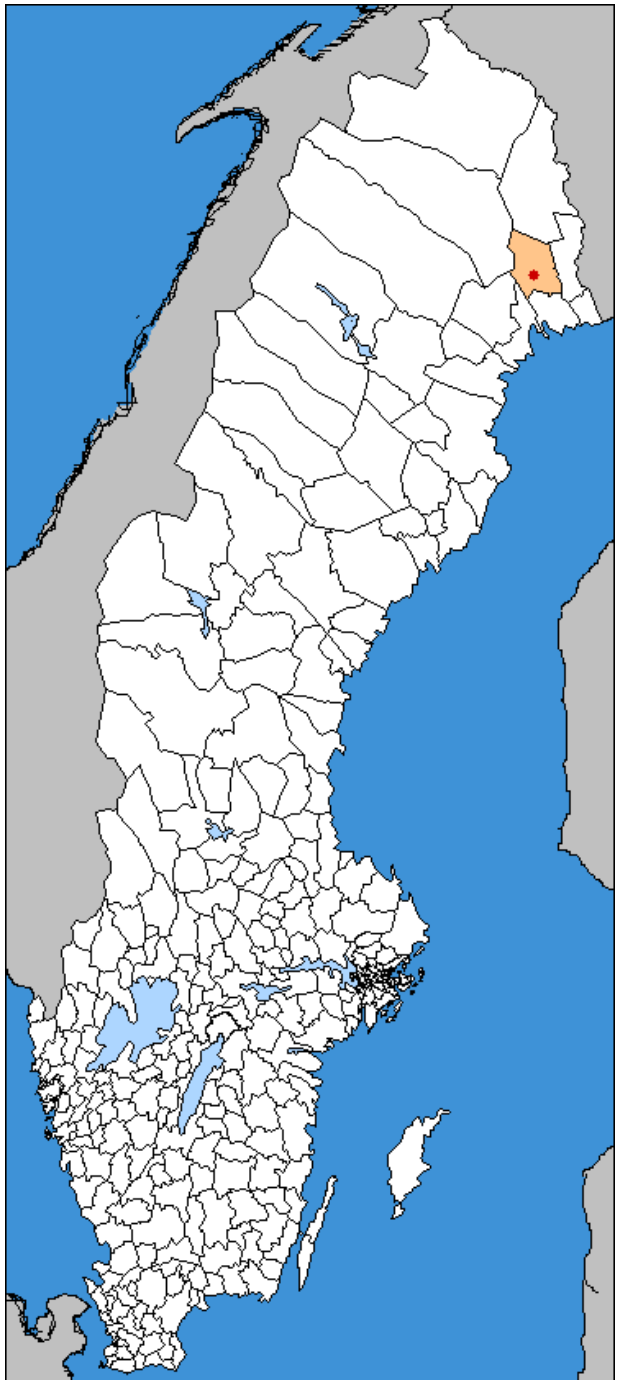
FDR < 0.05

CVD: community and domestic violence
IPV: intimate partner violence

	Depression [a]	*PTSD* [b]
	r	*r*
CORIN	0.11	0.14
CFTR	0.21*	0.20*
SMYD3	0.10	0.01
BARX1	0.09	0.00

PTSD: Post-traumatic stress disorder



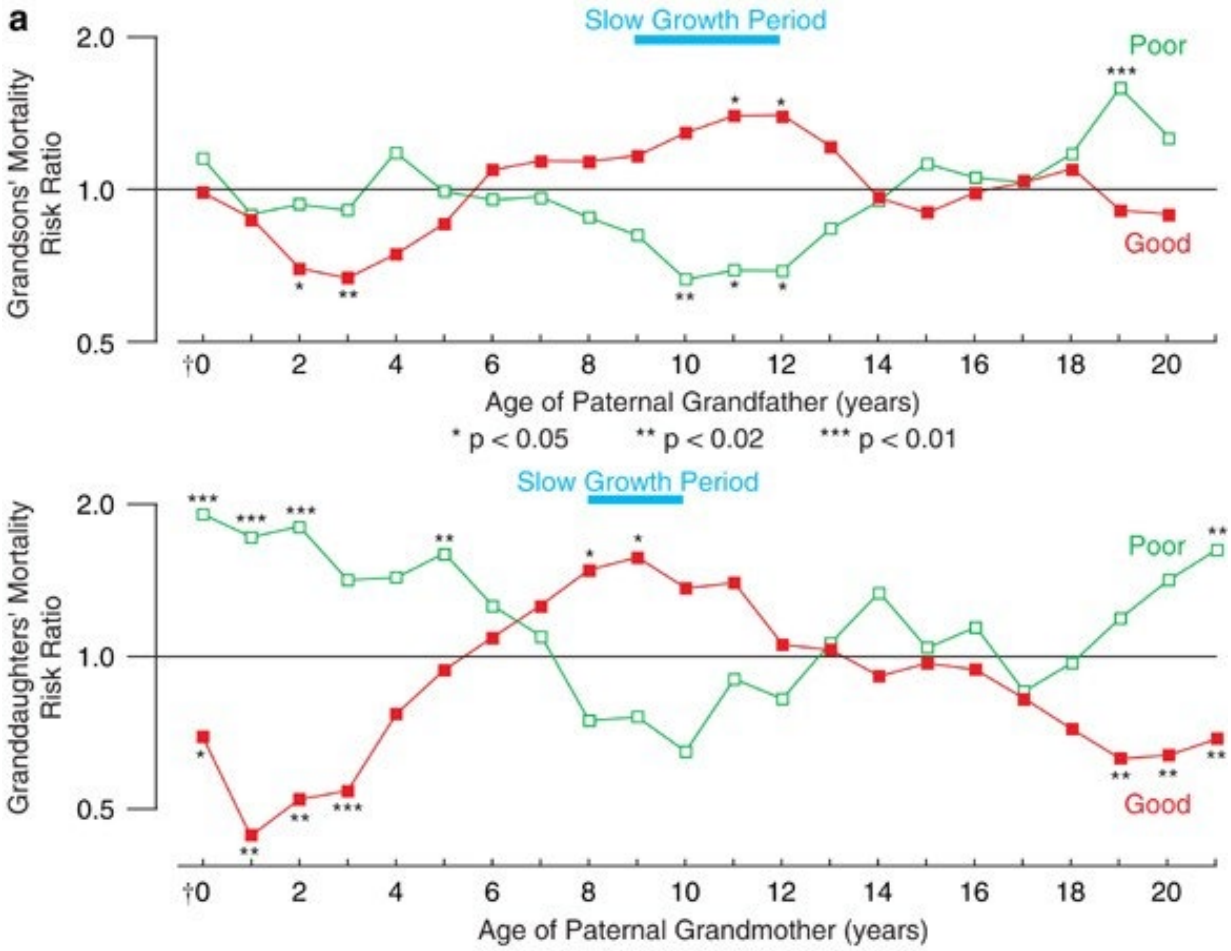


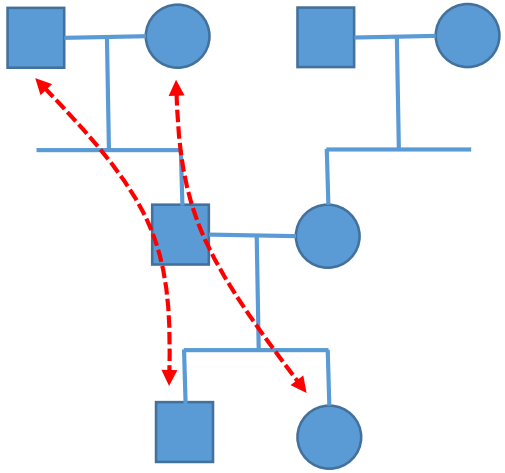
ÖVERKALIX (SWEDEN)

Dr. Lars Olov Bygren:

What effect do the feast and famine years have on the health of the children and grandchildren

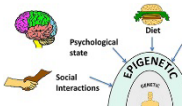
Sex-specific, male-line transgenerational responses in humans.
Pembrey et al., Eur. J. Hum. Genet. 2006.





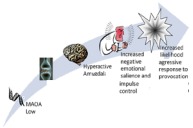
SUMMARY

EXTERNAL CONDITIONS



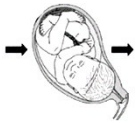
ORGANISM

EPIGENETIC VARIATION IN THE POPULATION



PRENATAL / EARLY / ADULT

Maternal stress
Famine/Feasting
Mental health

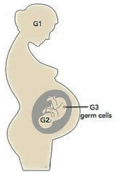


Licking of male pups
One child policy

Alcohol abuse
Cosmetics

ADJUSTED
GENE EXPRESSION

FIXED



CONSEQUENCES FOR THE PHENOTYPE AT LATER LIFE AND OFFSPRING