Epigenetics and Diseases

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OUTLINE

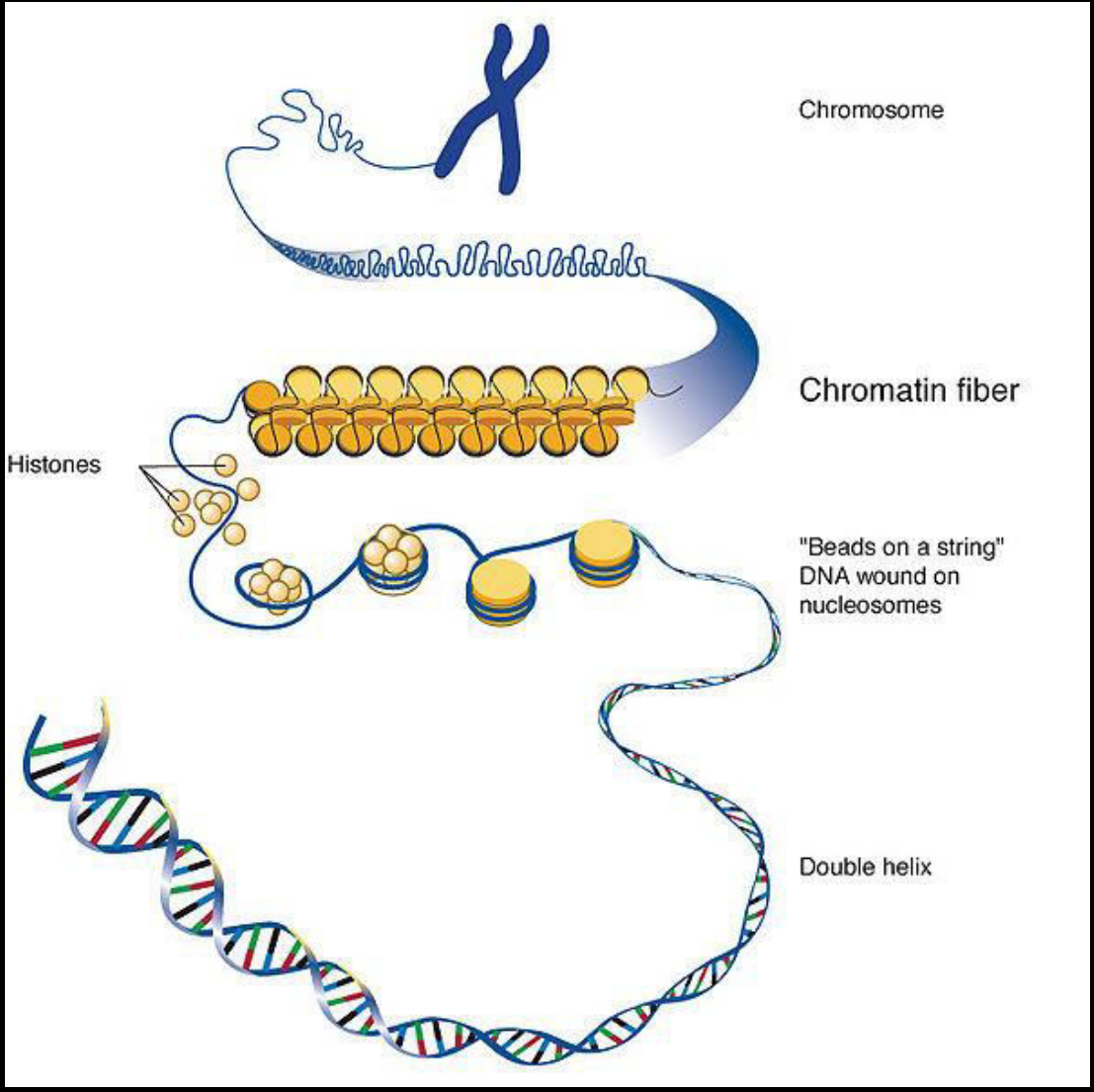
- Epigenetics, Epigenome, Epigenetic Changes and Imprinting.
- Epigenetic inheritance, Memory.
- Imprinting – epigenetics in expression of father and mother genes in the offspring and its relevance to phenotype and disease.
- Maternal diet during gestation and epigenetic changes – how mother's nutrition affects long term health of the child.
- Parental care and epigenetics – influence of parental care on epigenetic changes – stress, obesity, hypertension, CVD, IBS etc.,
- Child abuse and epigenetic changes - Suicide – human subject.
- Environmental effects on epigenetics – insight from study on Twins.
- Toxicants and epigenetics – its effects on future generation.
- Epigenetic Nanotherapeutics – Research Data.
- Epigenetic and Tumor Microenvironment.
- Take home message.

EPIGENETICS

Epi-genetics – study of heritable changes in the phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence.

Epi-genome – Genome with epigenetic modifications.

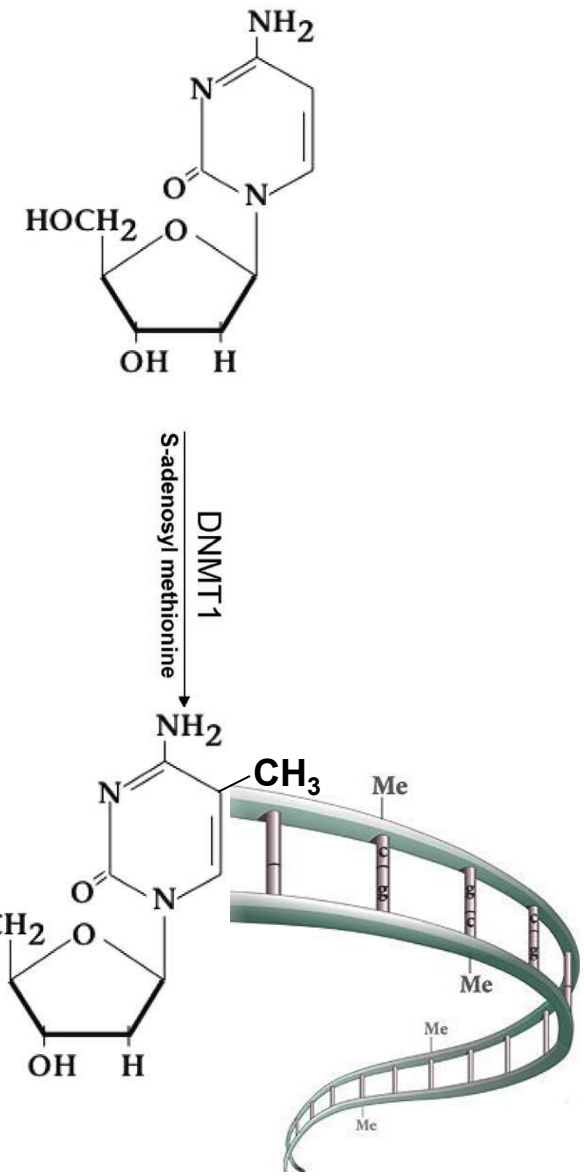
NUCLEOSOME – HISTONES AND DNA

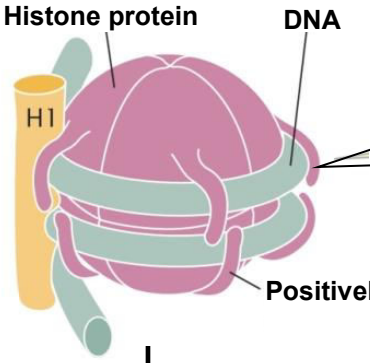


- Each base pair (bp) in DNA – 0.34 nm long.
- # of bp/cell – 6 million
- Each cell has - 2 m of DNA [$(0.34 \times 10^{-9}) \times (6 \times 10^{9})$]. Has to fit in nucleus 2-10 um in size.
- Human body has 50 trillion cells – 100 trillion m of DNA.
- Distance between sun and earth – 150 billion m
- Each of us has enough DNA to go from here to sun and come back more than 300 times.

Major epigenetic modifications – Methylation and Acetylation

2 – deoxycytidine

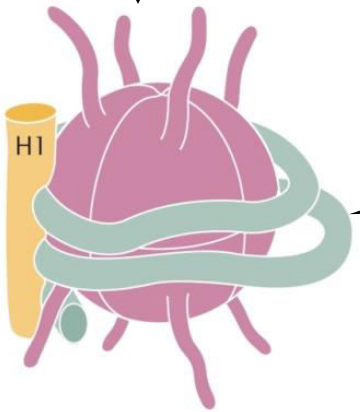




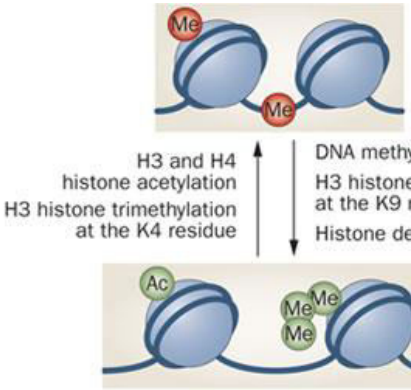
Positively charged tails of nucleosomal histone proteins probably interact with negatively charged phosphates of DNA

Positively charged tail

Acetylation



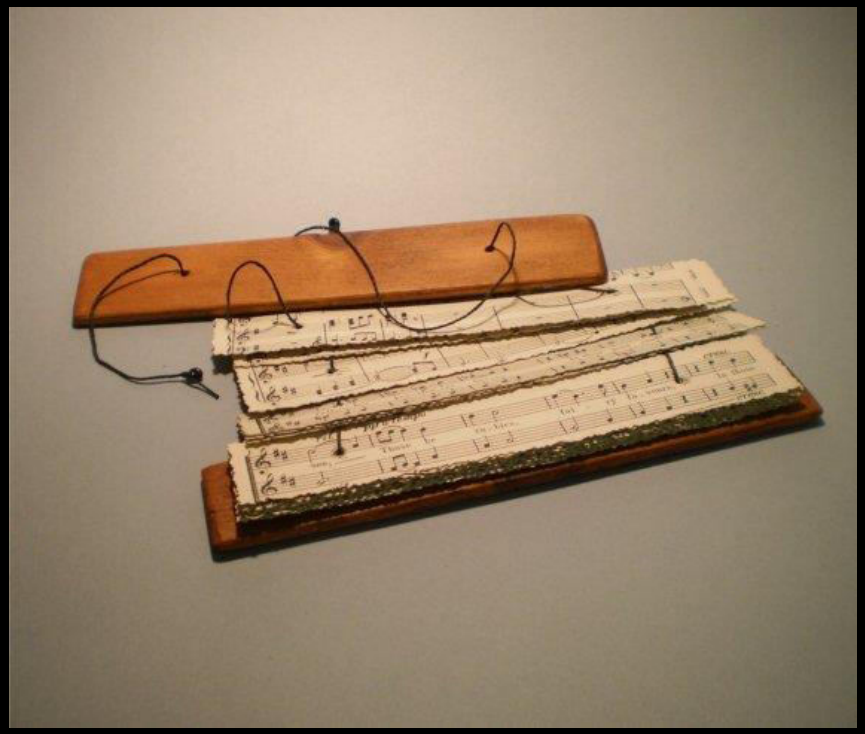
Acetylation of the tails weakens their interaction with DNA and may permit some transcription factors to bind to DNA

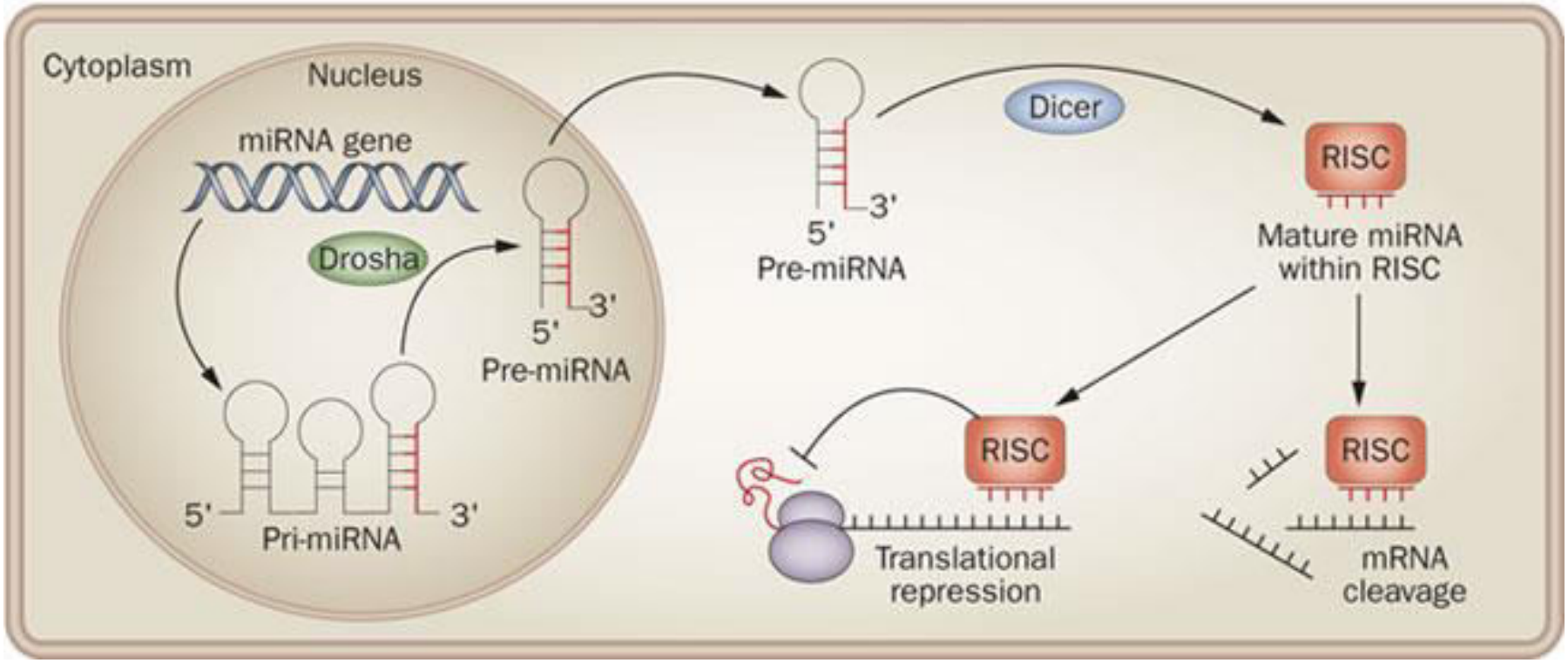


ANALOGUE FOR EPIGENETIC MODIFICATION

Deacetylation

Acetylation



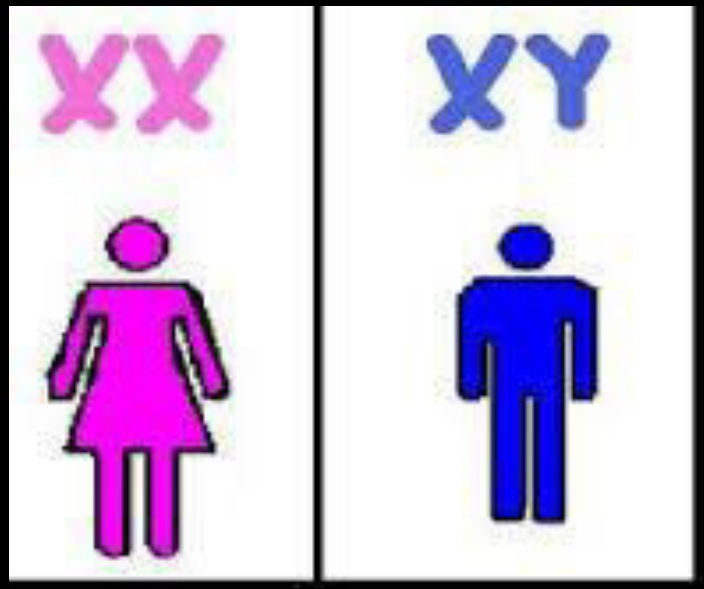


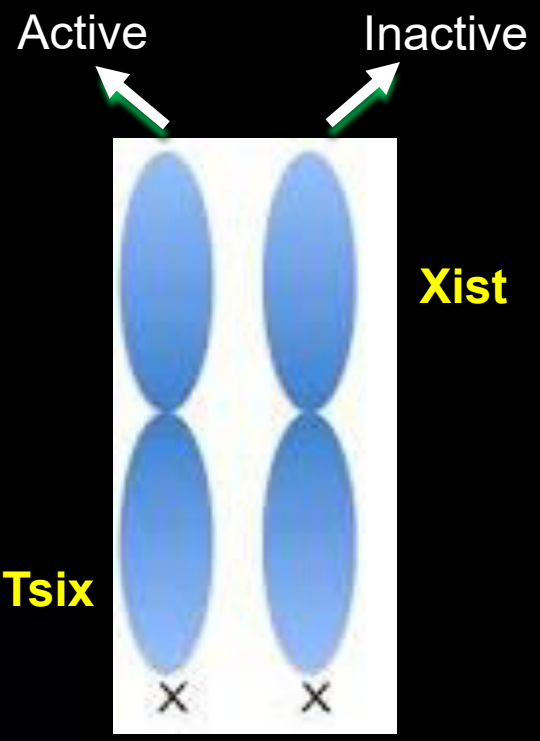
Dorsha

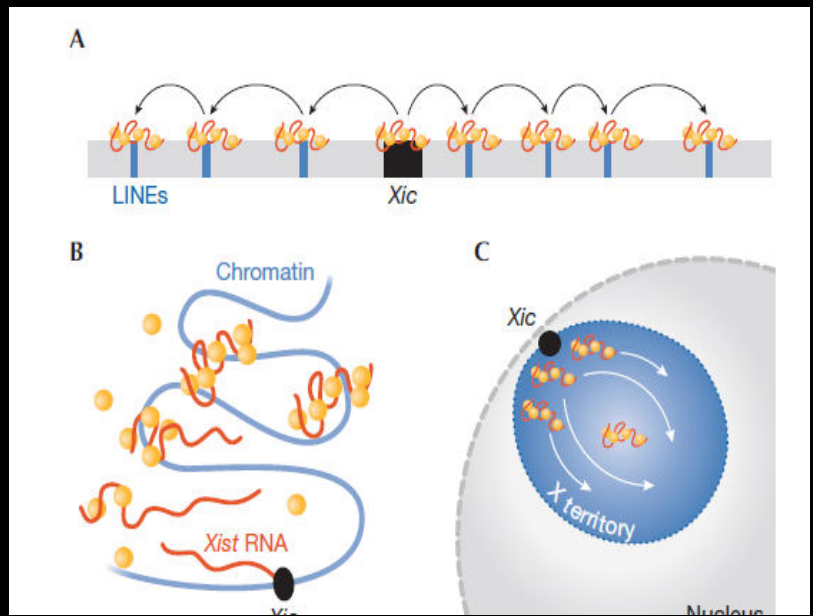
DGCR8 - Pasha

Microprocessor Complex

- Hsa- mir-196a2- Non small lung cancer
- miR-17 and miR-30c-1 – familial breast cancer


XX
XY


Active
Inactive
Xist
Tsix
X
X


A
LINEs
Xic
B
Chromatin
Xist RNA
C
Xic
X territory

Two type of X chromosomes – X - inactive (Xi), X active (Xa)

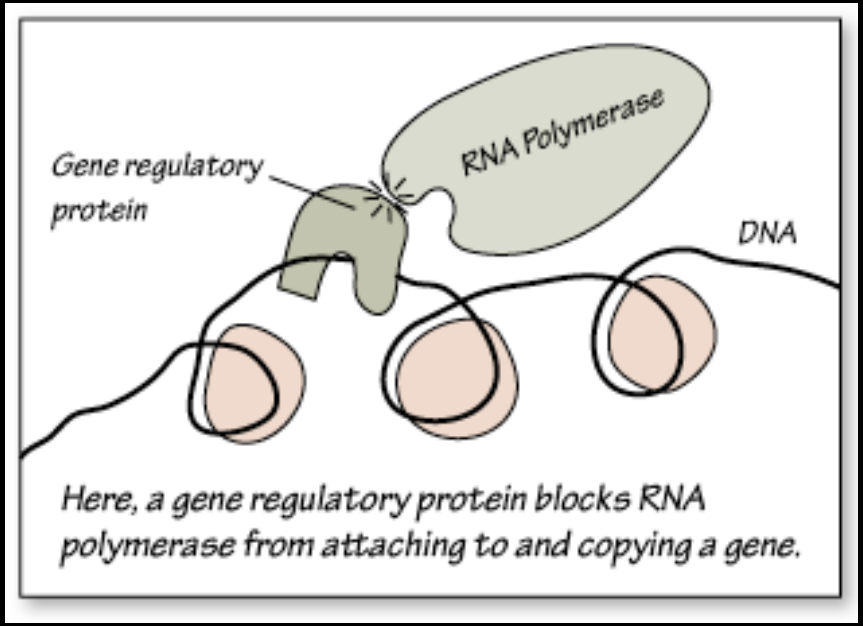
Two type of regulatory RNAs - Xist and Tsix RNAs

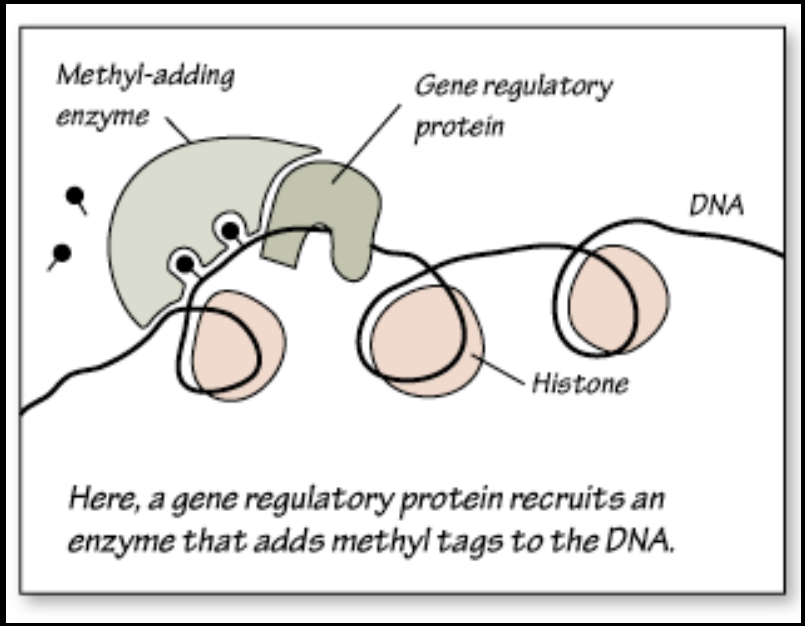
Xist RNA is a long non coding RNA produced by X chromosome which in future will be inactivated. This RNA sticks to the chromosome produced it and represses its gene function.

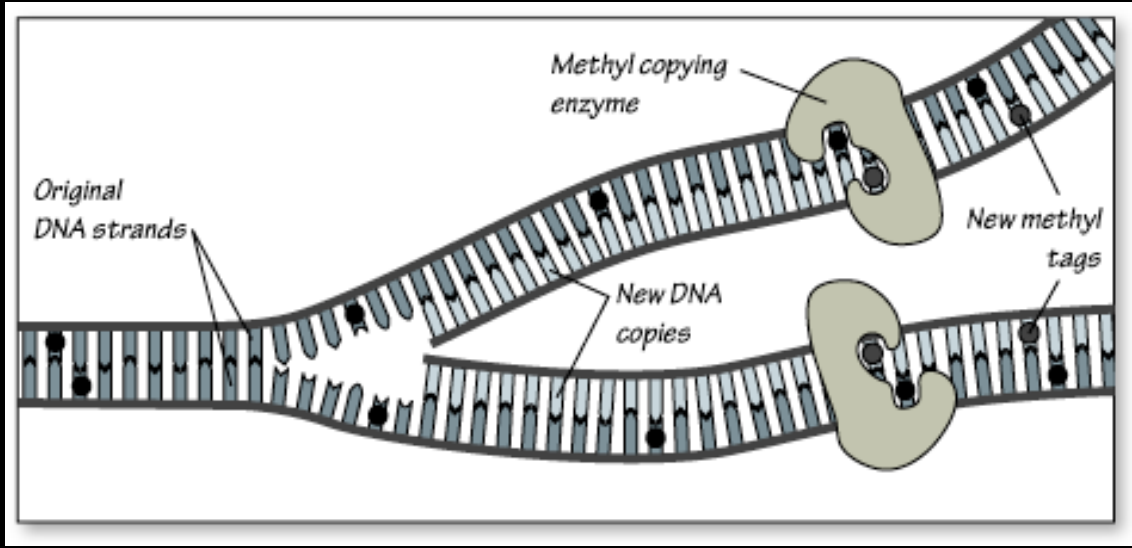
Xa RNA also initially produce this RNA but then stops its production

Tsix a negative regulator of Xist is produced by both the chromosomes initially and then suppressed in Xi chromosome but not in Xa chromosome, this produce higher copies of this RNA which will bind to antisense strand of the chromosome.

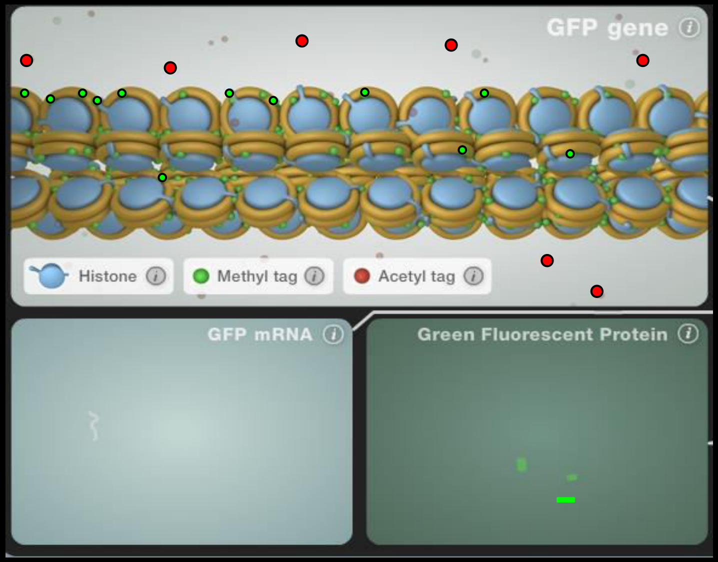
GENE REGULATORY PROTEIN AND GENE SILENCING

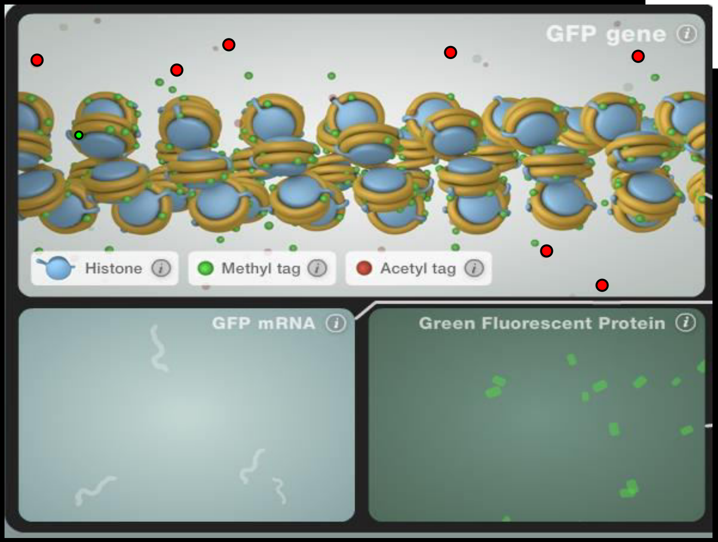


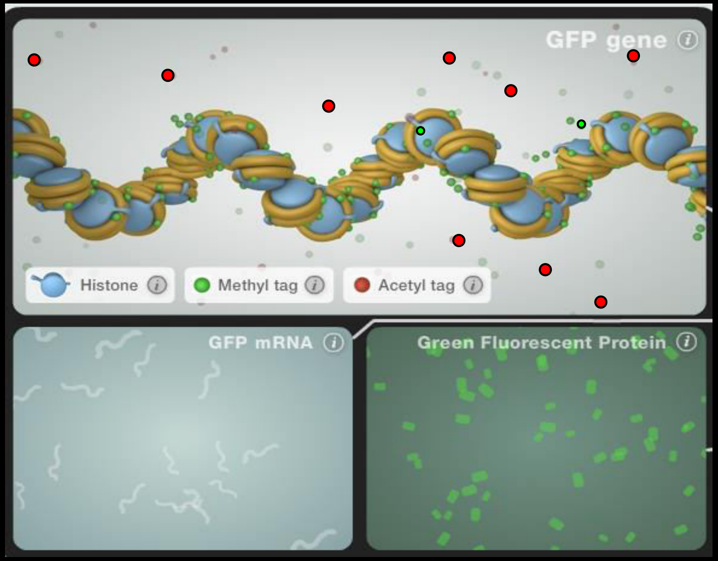


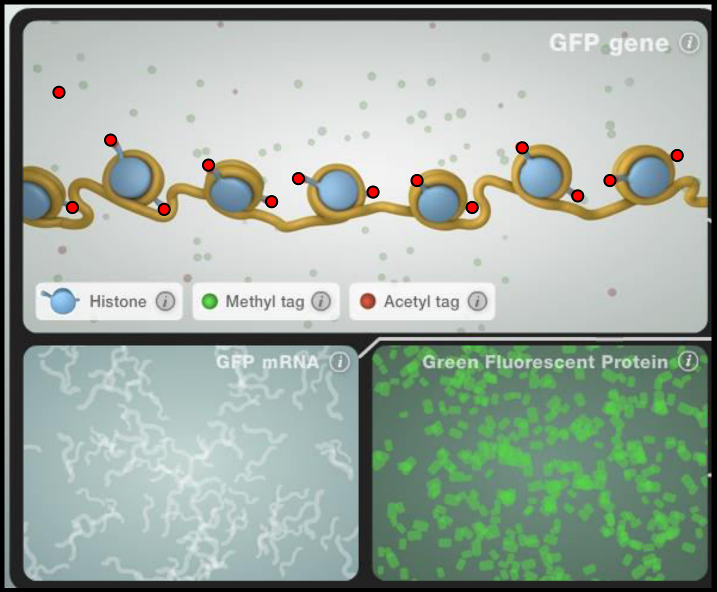


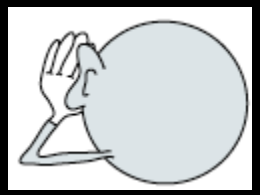
GENE EXPRESSION

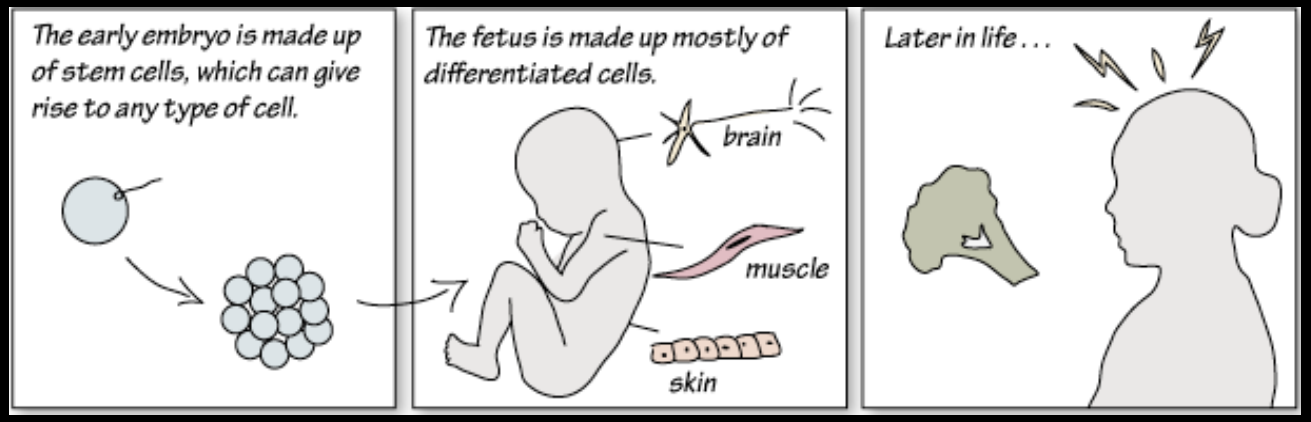


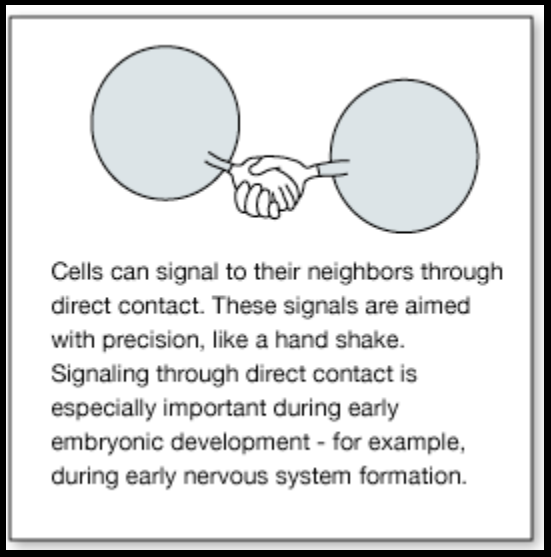


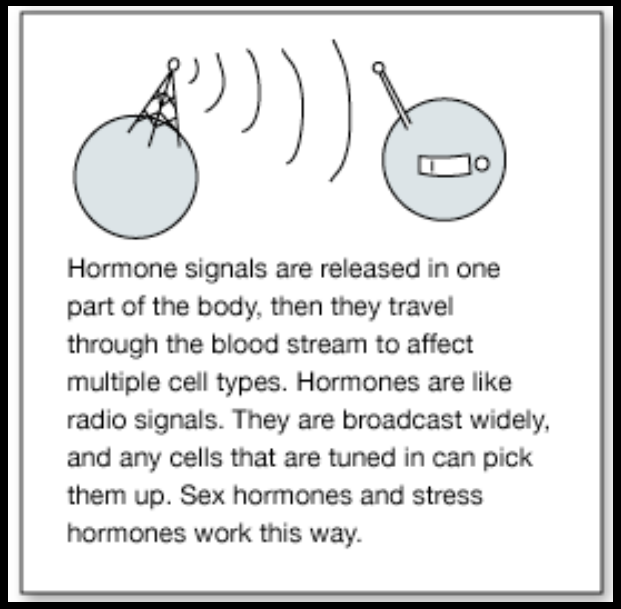


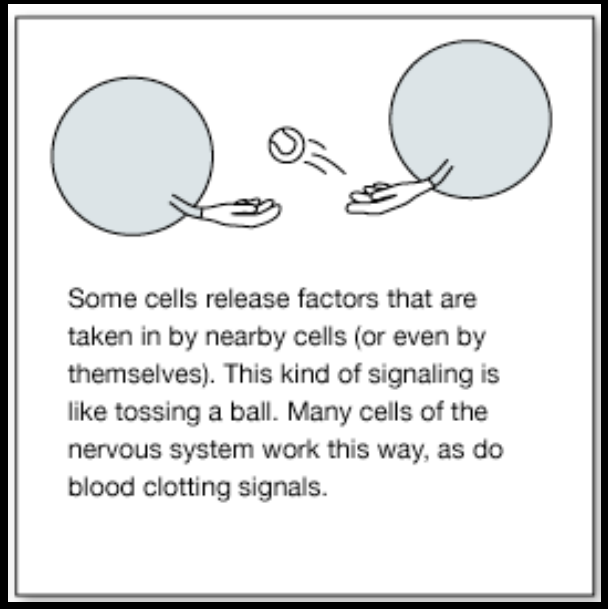


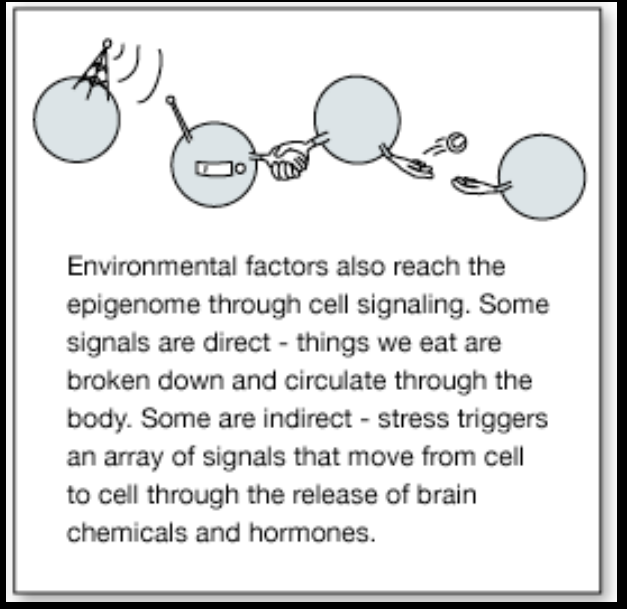



The early embryo is made up of stem cells, which can give rise to any type of cell.
The fetus is made up mostly of differentiated cells.
brain
muscle
skin
Later in life . . .

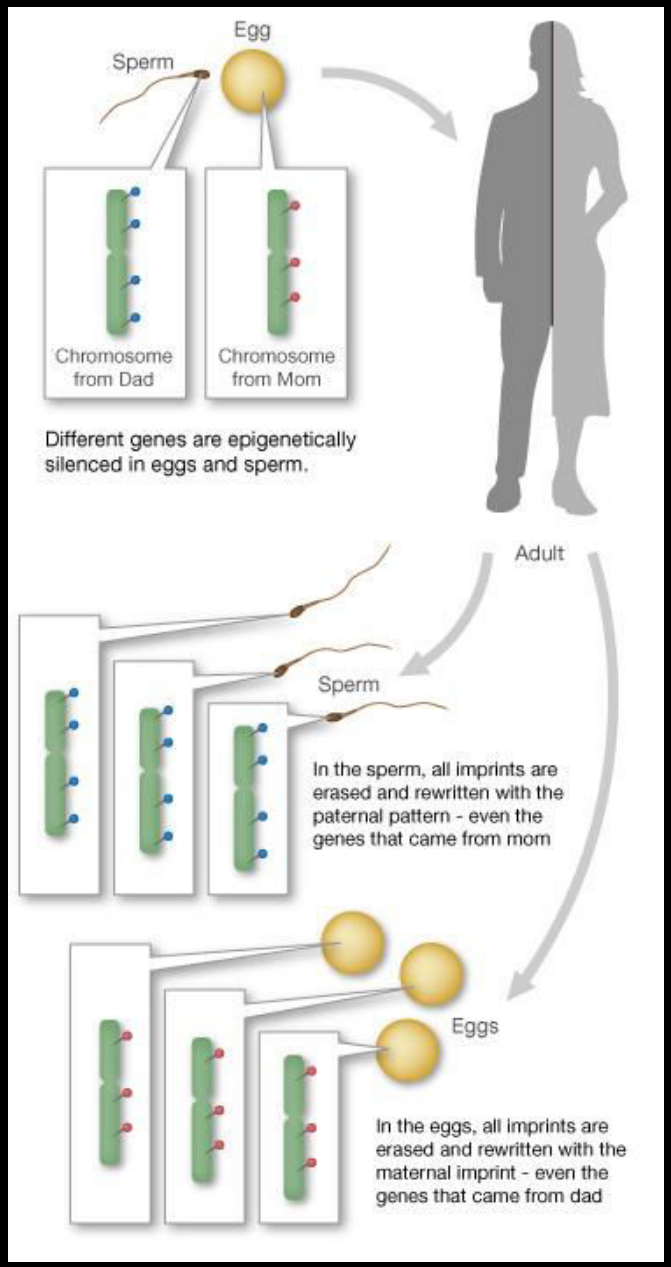

Cells can signal to their neighbors through direct contact. These signals are aimed with precision, like a hand shake. Signaling through direct contact is especially important during early embryonic development - for example, during early nervous system formation.


Hormone signals are released in one part of the body, then they travel through the blood stream to affect multiple cell types. Hormones are like radio signals. They are broadcast widely, and any cells that are tuned in can pick them up. Sex hormones and stress hormones work this way.


Some cells release factors that are taken in by nearby cells (or even by themselves). This kind of signaling is like tossing a ball. Many cells of the nervous system work this way, as do blood clotting signals.


Environmental factors also reach the epigenome through cell signaling. Some signals are direct - things we eat are broken down and circulate through the body. Some are indirect - stress triggers an array of signals that move from cell to cell through the release of brain chemicals and hormones.

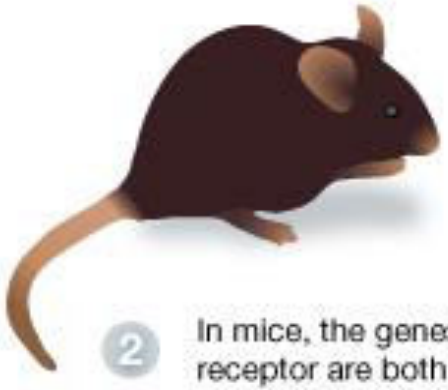
EPIGENETICS - IMPRINTING



Beckwith-Wiedemann Syndrome – An example of imprinting

AN EXAMPLE OF IMPRINTING

1 In mammals, the growth factor Igf2 interacts with the Igf2 receptor.



Genes from mom:
Igf2 receptor - ON
Igf2 - OFF

Genes from dad:
Igf2 receptor - OFF
Igf2 - ON

2 In mice, the genes for Igf2 and the Igf2 receptor are both imprinted.

Deleting the mother's Igf2 receptor gene produces overly large offspring.

Deleting the father's Igf2 gene produces dwarf offspring.

Deleting the mother's Igf2 receptor gene AND the father's Igf2 gene produces normally sized offspring.

3 The imprints on the Igf2 and Igf2 receptor genes normally cancel each other out. Changing the imprint on one copy of the gene has a dramatic effect on the size of the offspring. This result supports the genetic conflict hypothesis

ALTERING THE NATURAL ENVIRONMENT – INDUCES EPIGENETIC CHANGES

Am J Hum Genet. 2004 Sep; 75(3): 526–528.

Beckwith-Wiedemann Syndrome and IVF: A Case-Control Study

Jane Halliday,[1,3,4] Kay Oke,[5] Sue Breheny,[6] Elizabeth Algar,[1,3] and David J. Amor[1,2,3]

Loss of imprinting in chromosome 11 p 15. Major cause methylation of Igf2 receptor

Human over growth syndrome / Beckwith- weidemann syndrome.

The study done in Victoria state – Australia (1983 – 2003). 13, 16, 500 cases were investigated. 4/14,485 IVF had BWS.

The risk for BWS is 18 times higher in IVF babies than normally conceived babies

Most of the genes turn off in the egg when they are removed from their natural environment – Mouse embryo genes turned off in the petri dish. The same technique as IVF.

Am J Hum Genet. 2003 Jan; 72(1): 156–160.
Published online 2002 Nov 18. doi: 10.1086/346031
PMCID: PMC378620

Association of In Vitro Fertilization with Beckwith-Wiedemann Syndrome and Epigenetic Alterations of *LIT1* and *H19*

Michael R. DeBaun,[1] Emily L. Niemitz,[2] and Andrew P. Feinberg[2]

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Intracytoplasmic Sperm Injection May Increase the Risk of Imprinting Defects

Gerald F. Cox,[1,2,*,†] Joachim Bürger,[3,*,‡] Va Lip,[1] Ulrike A. Mau,[4] Karl Sperling,[3] Bai-Lin Wu,[1,2] and Bernhard Horsthemke[5]

[1]Children's Hospital and [2]Harvard Medical School, Boston; [3]Institut für Humangenetik, Charité, Humboldt Universität zu Berlin, Berlin; [4]Institut für Humangenetik, Eberhard-Karls-Universität, Tübingen, Germany; [5]Institut für Humangenetik, Universität Essen, Essen, Germany

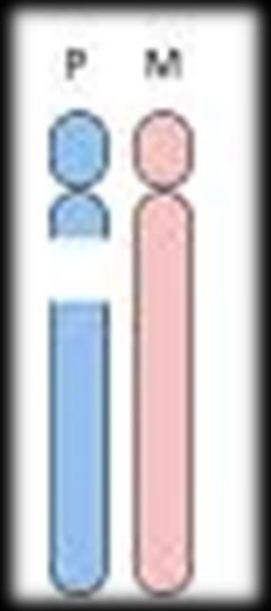
In germ cells and the early embryo, the mammalian genome undergoes widespread epigenetic reprogramming. Animal studies suggest that this process is vulnerable to external factors. We report two children who were conceived by intracytoplasmic sperm injection (ICSI) and who developed Angelman syndrome. Molecular studies, including DNA methylation and microsatellite and quantitative Southern blot analysis, revealed a sporadic imprinting defect in both patients. We discuss the possibility that ICSI may interfere with the establishment of the maternal imprint in the oocyte or pre-embryo.

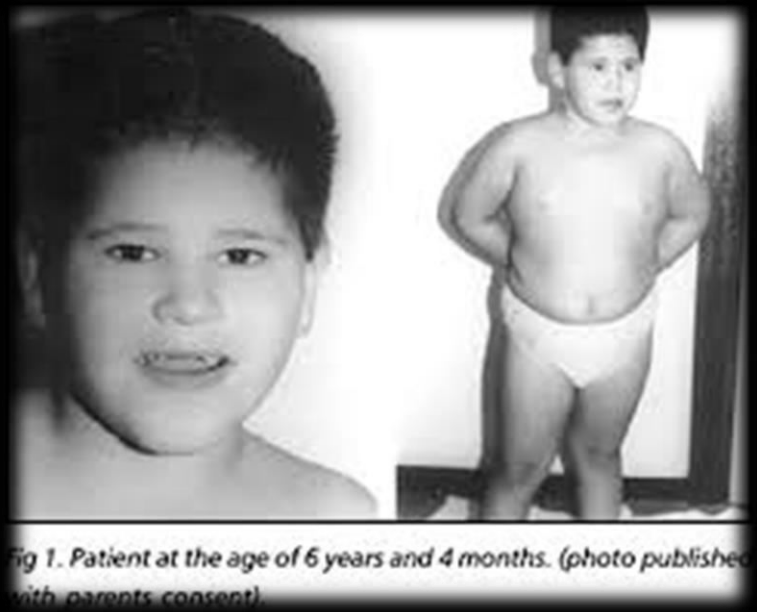
Genes have the memory from where they came from

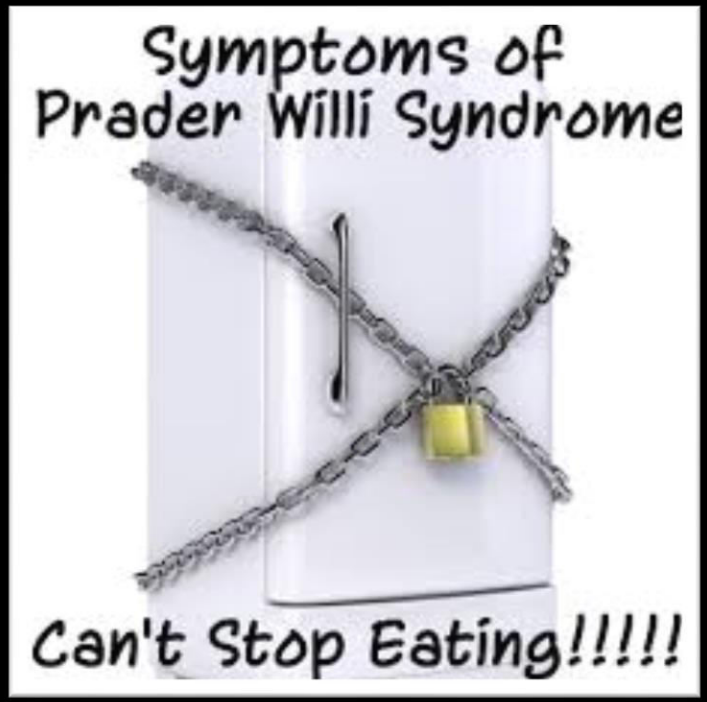
Prader wili syndrome – Chromosome 15 – father

Angelman syndrome – chromosome 15 – mother

How do they know ???

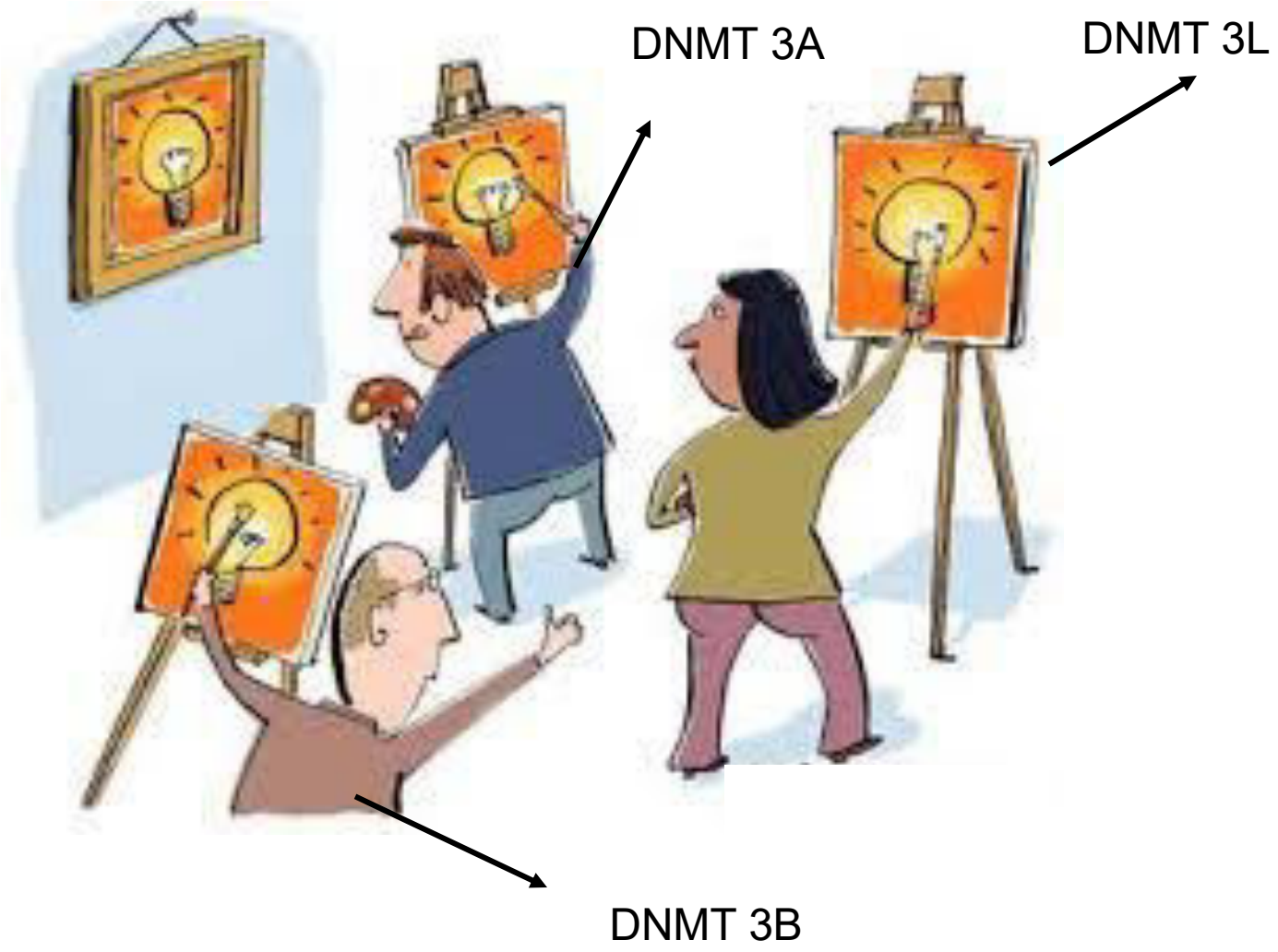




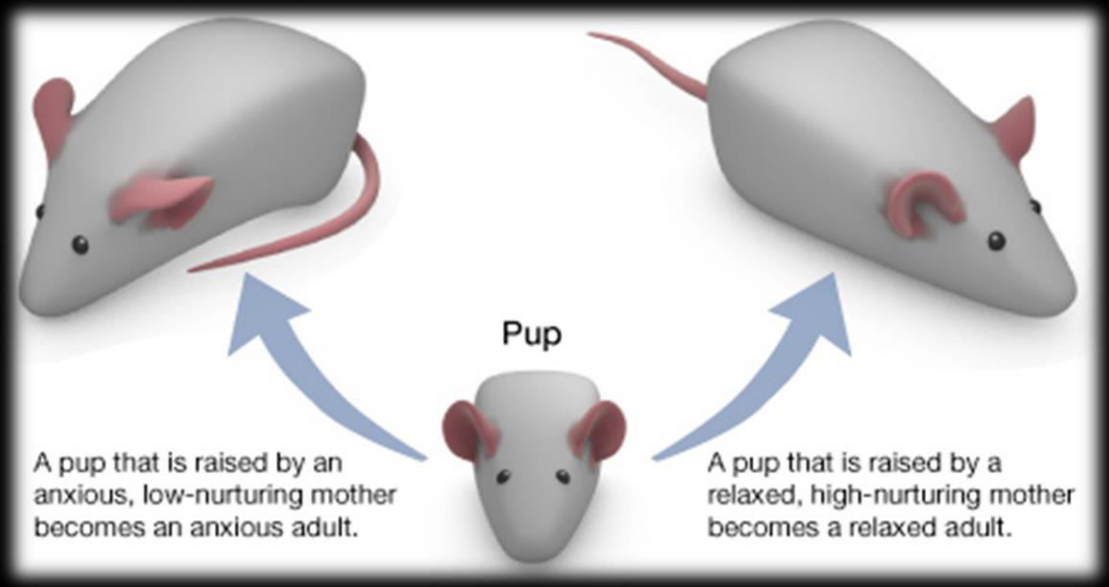


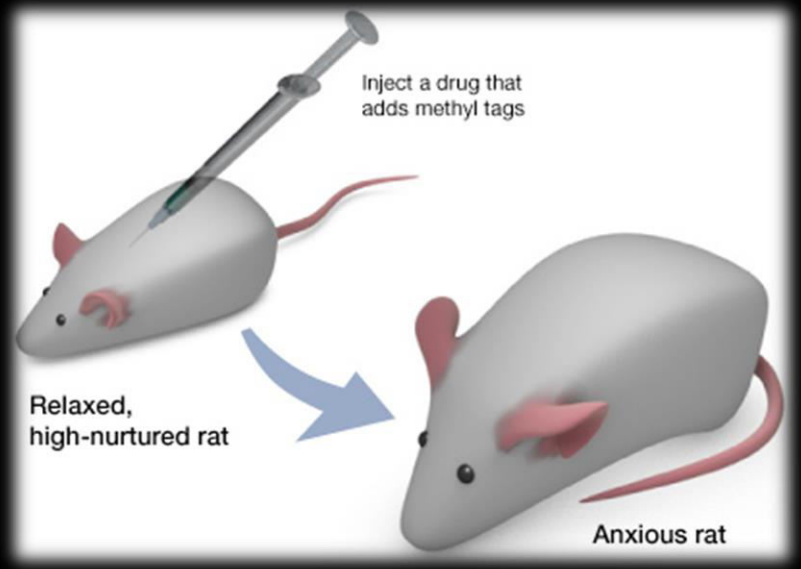
Faithful copiers – DNMT 3A, 3B and 3L

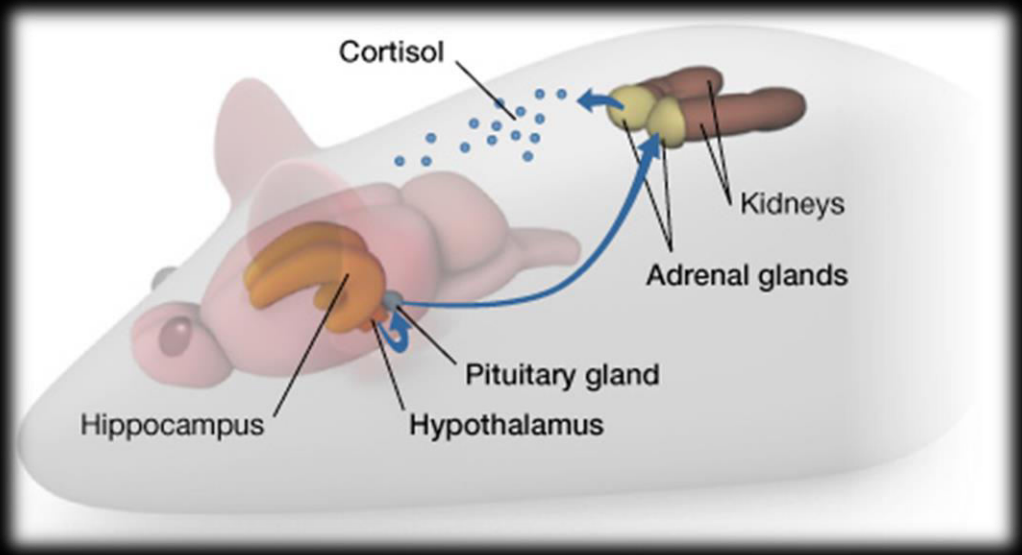
Only one copy – cannot be lost



MATERNAL CARE AND EPIGENETIC CHANGE







Epigenetic correlates of neonatal contact in humans

Published online by Cambridge University Press: **22 November 2017**

1,000 mother-infant pairings were recruited in the Vancouver, BC, Canada area.

Conclusion

The study concluded that a child's DNA methylation signature, also known as epigenetic expression, is altered by a mother's contact, which mean's that when your mother hugs you, it can literally change the expression of your own DNA. I mean...come on!

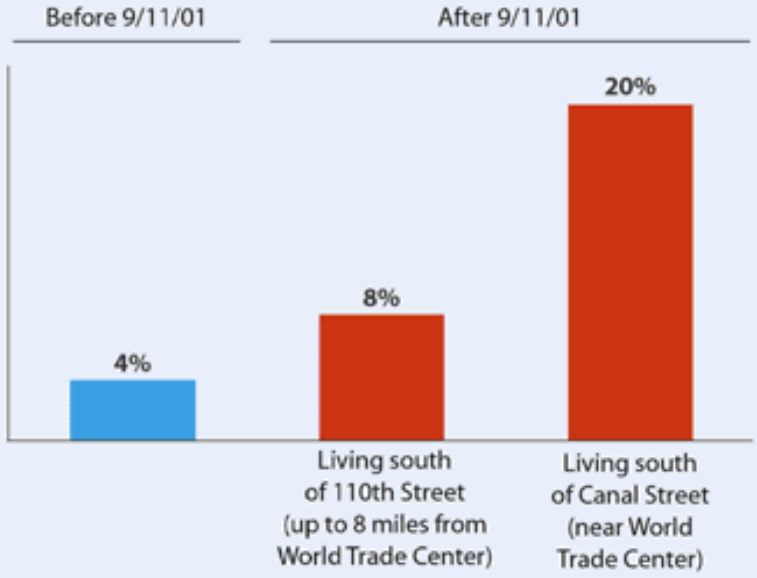
A potential delay in development was also found. The study determined that a child's development is negatively inhibited or slowed when high distress is met with a response of low contact from the mother. Within the study, this delay in development was called a negative epigenetic age deviation.

As integrative medicine will continue to integrate evidence, knowledge like this will continue to shape our future. In this case, you may have always known that there is nothing better than a hug from your mother when you need it the most, but now...well, there's science to back it up.

Disasters induced epigenetic changes – can become imprint in the gene for generations

PTSD incidence increases in Manhattan after 9/11/01

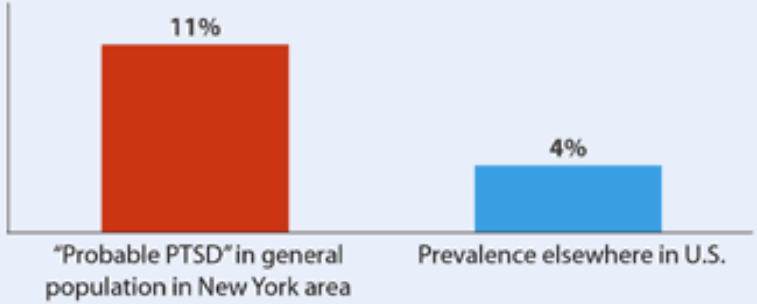
Members of general public reporting symptoms consistent with PTSD diagnosis



Pre-Sept. 11 prevalence based on 1999 HHS national benchmark study.
Post-Sept. 11 prevalence based on questionnaires given 5 to 8 weeks after Sept. 11.

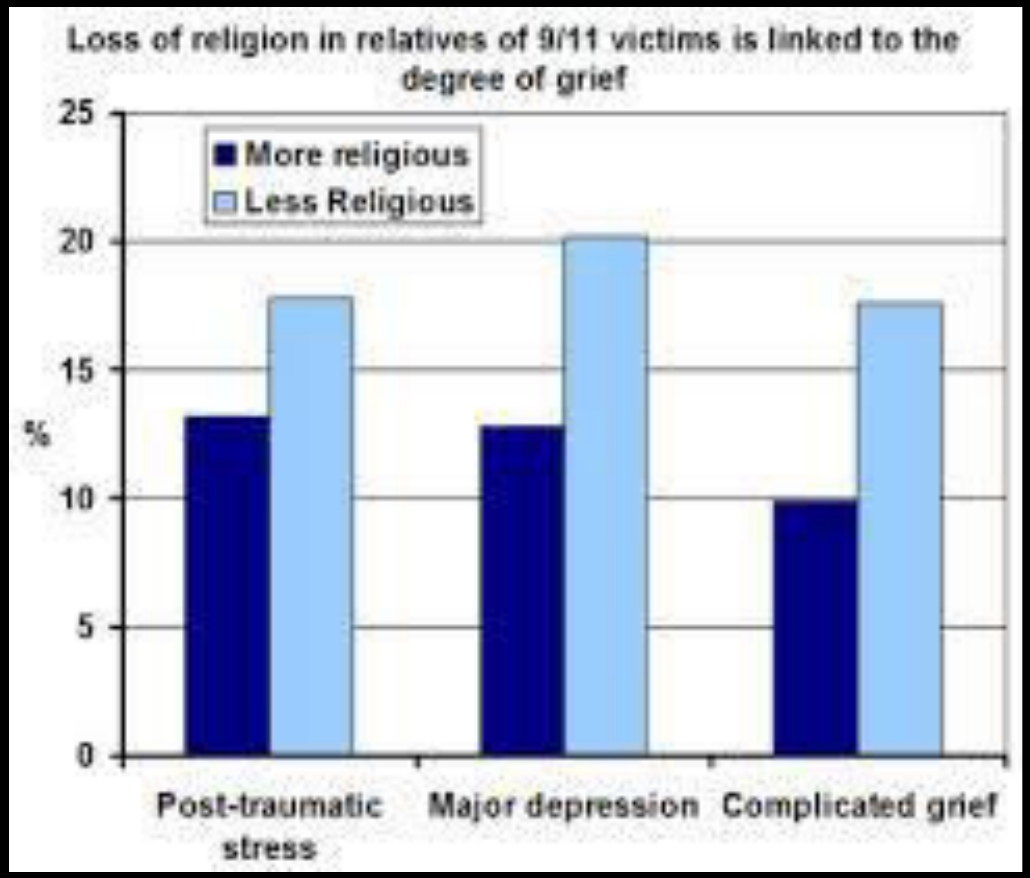
SOURCE: GALEA S, ET AL. *N ENGL J MED*. 2002;346(13):982–987.

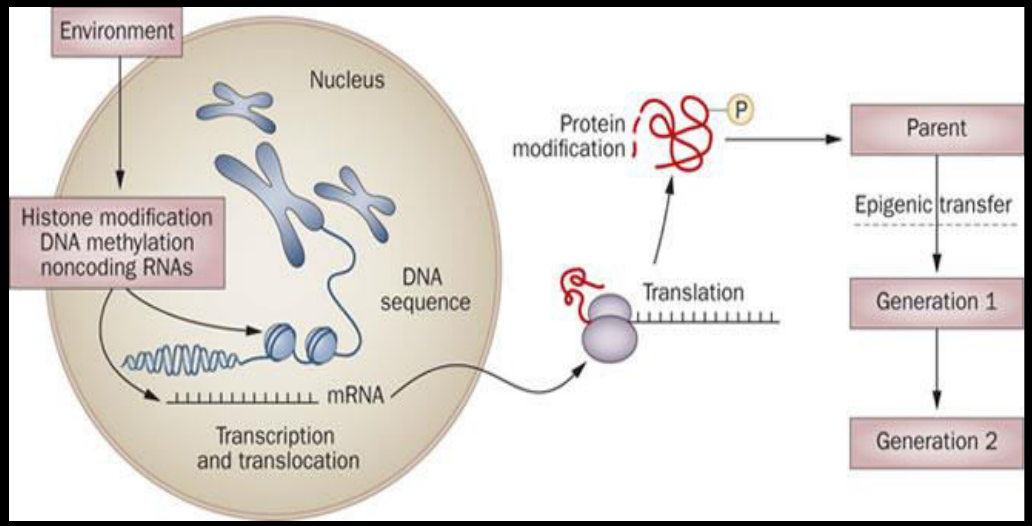
PTSD more common in New York after 9/11



Authors used the term "probable PTSD" because their assessment was based on screening instruments, not physician evaluations.

SOURCE: SCHLENGER W, ET AL. *JAMA*. 2002;288:581–588.





Nat Rev Gastroenterol Hepatol. 2010 Aug;7(8):465-71. doi: 10.1038/nrgastro.2010.99. Epub 2010 Jun 29.

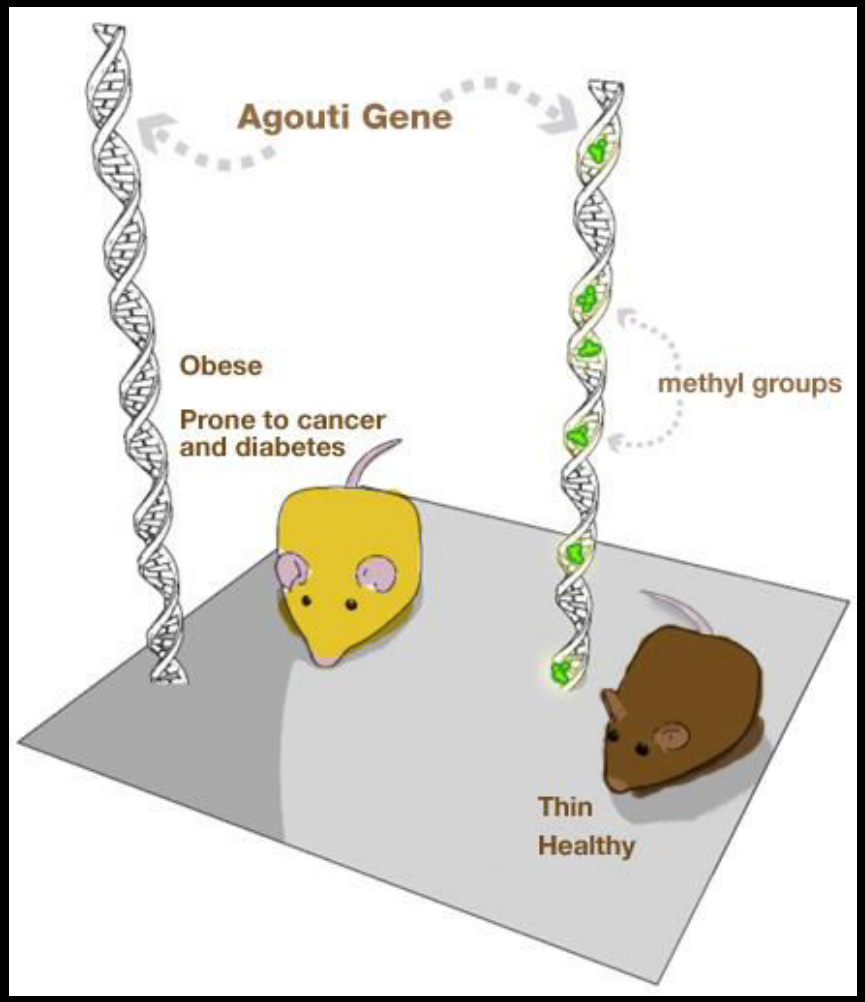
IBS: An epigenetic perspective.

Dinan TG[1], Cryan J, Shanahan F, Keeling PW, Quigley EM.

Abstract

IBS is a common and debilitating disorder. The pathophysiology of IBS is poorly understood and is currently viewed as a biopsychosocial disorder with symptoms mediated via the brain-gut axis. Epidemiological studies of IBS point to risk factors such as familial clustering, sexual abuse and other forms of childhood trauma, low birth weight and gastrointestinal infection. Epigenetics focuses on the complex and dynamic interaction between the DNA sequence, DNA modifications and environmental factors, all of which combine to produce the phenotype. Studies in animal models of early stress and in humans who have experienced childhood trauma or abuse suggest that these events can lead to long-lasting epigenetic changes in the glucocorticoid receptor gene brought about by hypermethylation of a key regulatory component. Animal studies also indicate that the microbiota has a pivotal role in programming the core stress system, the hypothalamic-pituitary-adrenal axis and the immune system through epigenetic mechanisms. In this Perspectives, an epigenetic model of IBS is presented that incorporates many of the current findings regarding IBS, including proinflammatory markers, neuroendocrine alterations and links with both psychosocial stress and stress related to infection. We conclude that applying epigenetic methodology to this common and disabling disorder may help unravel its complex pathophysiology and lead to more effective treatments.

DNA IS NOT DESTINY



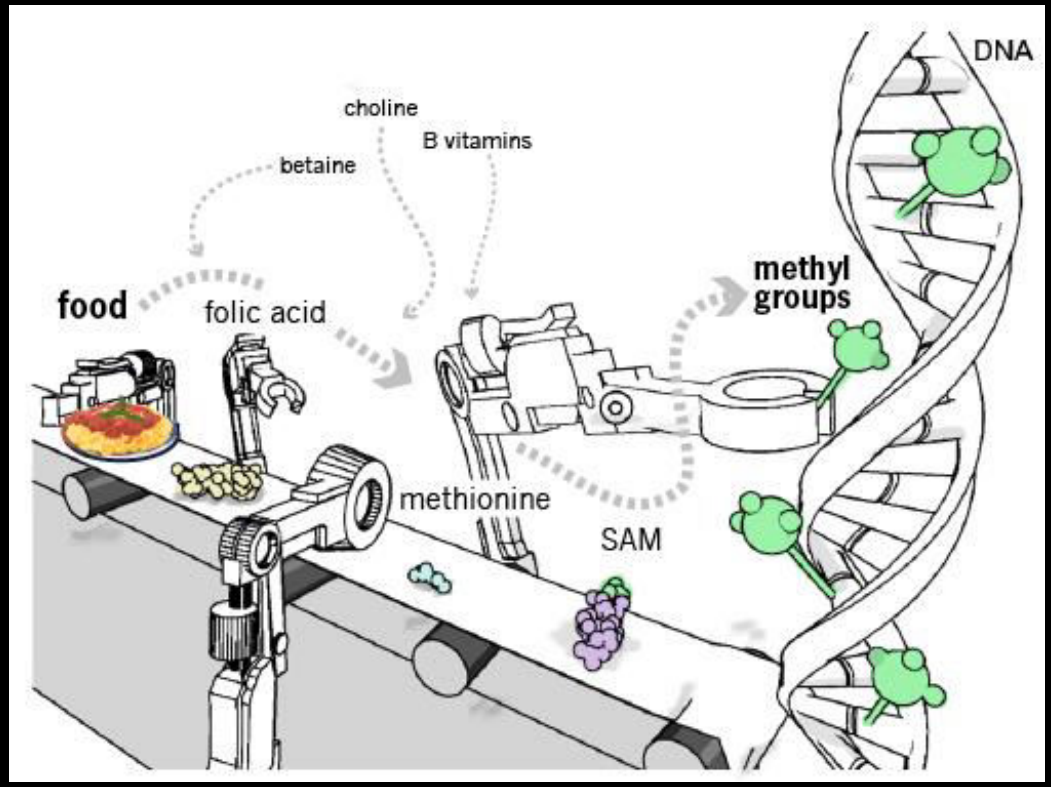
Randy Jirtle and Robert Waterland

Dept of Radiation Oncology, Duke University; 2000

vitamin B12, folic acid, choline and betaine

Published online 4 August 2003 | Nature | doi:10.1038/news030728-12

NUTRITION AND EPIGENOME



Eating for two

Foods rich in folate (vitamin B9) including leafy green vegetables, citrus fruits and strawberries, are dietary sources of methyl.

Vitamin B12, found in fish, meat, milk and eggs, can donate methyl groups to the metabolism

Diet during pregnancy and early life – epigenetic changes and disease susceptibility

Dutch hunger winter (1944) in German occupied Netherlands – 18,000 died of hunger.

Individuals whose mothers were exposed to famine during first trimester of pregnancy exhibited increased risk of obesity and CVD.

Individuals whose mothers were exposed to famine at later stages of gestation had increased incidence for insulin resistance and hypertension.

Cohorts study in developed and developing nations, including the United Kingdom, North America, India and China have shown consistently that lower birth weight within the normal range for a particular population is associated with an increased risk in later life of CVD and the metabolic syndrome (hypertension, insulin resistance, type 2 diabetes, dyslipidaemia and obesity). Most of the studies linked causes due to IGF2 methylation

Dutch Hunger

Probands in their middle age had higher levels of triglycerides and LDL cholesterol. They also experienced higher rates of conditions such as obesity, diabetes and schizophrenia.

An explanation for these findings is that famine may cause life-long changes in DNA demethylation and subsequently increase blood lipid levels in late life. The Dutch famine studies have reported that participants exposed to famine up to 6 months during gestation had different methylation level in late adulthood at the *IGF2*, *INSIGF*, *IL10*, *LEP*, *ABCA1*, *GNASAS*, and *MEG3* gene loci, compared to their sex-matched siblings without famine exposure

Chinese Famine study - provide a **novel evidence that methylation in the *IGF2* gene** was positively associated with TC in late adulthood. The findings not only help to understand the function of *IGF2* but aid in delineating the mechanisms of cholesterol metabolism.

Gene – knockout studies in experimental mice produced similar results.

Mexican – American study – prenatal sugar and high fat rich food – resulted in IGF2 methylation and drawn similar conclusions

Thus infants born with lower body weight likely to have reduced fat mass and they undergo early catch-up growth resulting in greater accumulation of fat mass relative to lean body mass and they have increased risk of becoming obese than infants born with higher birth weights.

Formula milk fed infants show cardio-metabolic diseases in later life. Number of studies shown greater incidence of obesity in adults who were formula fed as opposed to breast fed during infancy.

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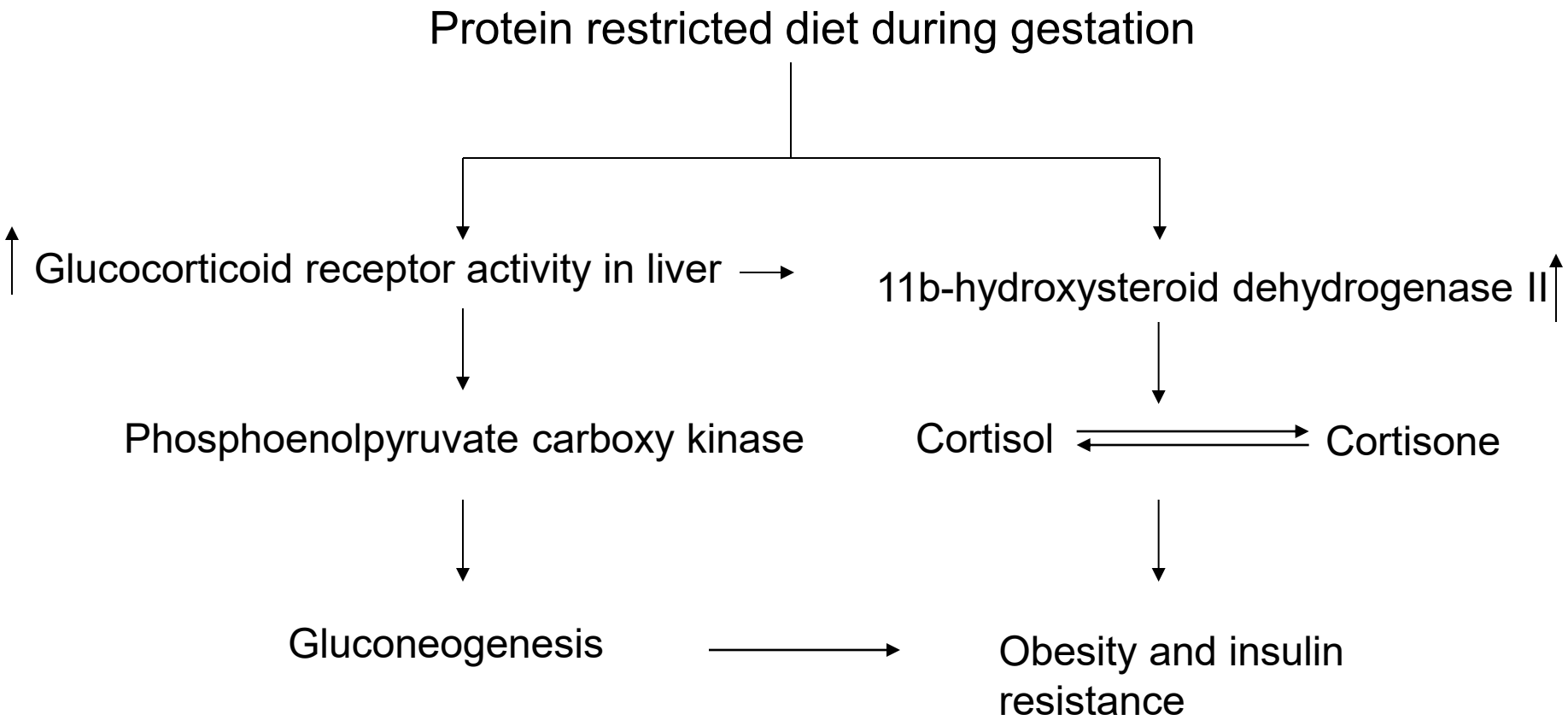
Early-life exposure to severe famine is associated with higher methylation level in the *IGF2* gene and higher total cholesterol in late adulthood: the Genomic Research of the Chinese Famine (GRECF) study


Protein restricted diet during gestation
Glucocorticoid receptor activity in liver
11b-hydroxysteroid dehydrogenase II
Phosphoenolpyruvate carboxy kinase
Cortisol
Cortisone
Gluconeogenesis
Obesity and insulin resistance

Maternal diet and aging alter the epigenetic control of a promoter–enhancer interaction at the Hnf4a gene in rat pancreatic islets

PNAS; Feb 11, 2011; Dr Susan Ozanne; Institute of metabolic science; Univ. of Cambridge, UK)

Hepatocyte nuclear factor 4-α (HNF-4α), is a transcription factor required for pancreatic β-cell differentiation and glucose homeostasis.

This study had shown that HNF-4α, which has been implicated in the etiology of type2 diabetes is epigenetically regulated by maternal diet.

Aging leads to progressive epigenetic silencing of the entire Hnf4a locus in islets, an effect that is more pronounced in rats exposed to a poor maternal diet.

Finding of this study provide evidence for environmentally induced epigenetic changes at the Hnf4a enhancer that alter its interaction with the P2 promoter, and consequently determine T2D risk.

Authors of this study proposed that environmentally induced changes in promoter-enhancer interactions represent a fundamental epigenetic mechanism by which nutrition and aging can influence long-term health.

“Type II diabetes, heart disease due to obesity, insulin resistance, and hypertension are the diseases most strongly associated with maternal diet during pregnancy,” said Karen Lillycrop, who specializes in perinatal nutrition at the University of Southampton in the UK.

Endocrinology. 2010 Oct; 151(10): 4756–4764.
Published online 2010 Aug 4. doi: 10.1210/en.2010-0505
PMCID: PMC2946145

Maternal High-Fat Diet Alters Methylation and Gene Expression of Dopamine and Opioid-Related Genes

Maternal obesity and consumption of a high-fat (HF) diet during pregnancy and lactation has been shown to increase the risk for development of obesity and related metabolic disorders in the offspring.

Animal studies have shown that maternal consumption of a palatable diet can increase the preference for fat and sugar in the offspring. The results were extended to human studies with 4,000 subjects.

Overall, data from this work show that maternal consumption of HF diet during pregnancy and lactation can program an increased drive for the consumption of palatable foods.

Don't count Dad out

LONGEVITY DETERMINED BY PATERNAL ANCESTORS' NUTRITION DURING THEIR SLOW GROWTH PERIOD

Social circumstances often impinge on later generations in a socio-economic manner, giving children an uneven start in life. Overfeeding and overeating might not be an exception. The pathways might be complex but one direct mechanism could be genomic imprinting and loss of imprinting. An intergenerational "feedforward" control loop has been proposed, that links grandparental nutrition with the grandchild's growth. The mechanism has been speculated to be a specific response, e.g. to their nutritional state, directly modifying the setting of the gametic imprint on one or more genes. This study raises the question: Can overnutrition during a child's slow growth period trigger such direct mechanisms and partly determine mortality?

Data were collected by following-up a cohort born in 1905 in Överkalix parish, northernmost Sweden. The probands were characterised by their parents' or grandparents' access to food during their own slow growth period. Availability of food in the area was defined by referring to historical data on harvests and food prices, records of local community meetings and general historical facts.

If there was a surfeit of food in the environment when the paternal grandfather was a 9-12 year old boy a shortening of the proband survival could be demonstrated. The influence of parents', maternal grandparents' and paternal grandmothers' access to food during their slow growth period was discounted in a multivariable analysis. The results are indicative of very early programming mechanisms in human adaptation to the social environment.

Difference in survival was 32 yrs

The study was of 303 probands, 164 men and 139 women, born in 1890, 1905, or 1920, and their 1,818 children and grandchildren. 44 were still alive in 1995 when mortality follow-up stopped.

Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period

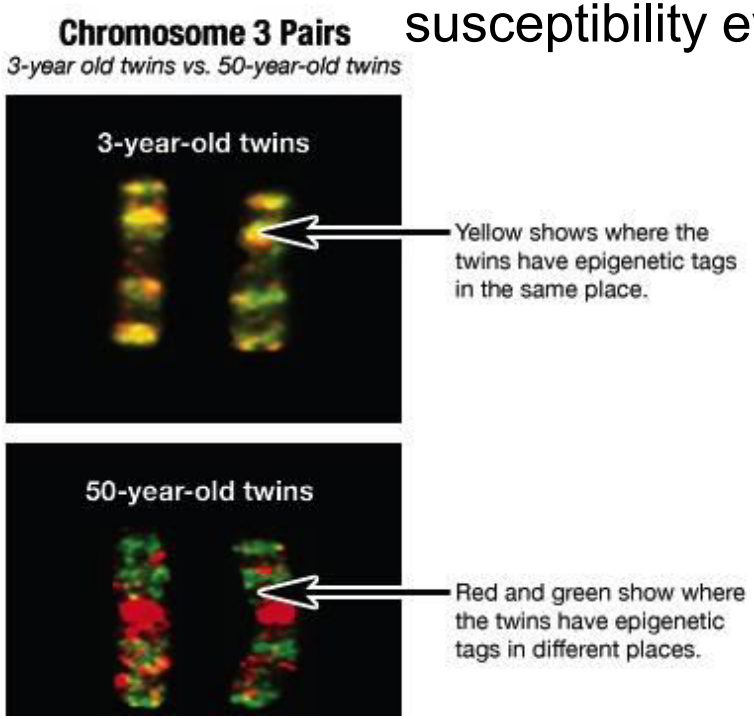
Overfeeding and overeating in families are traditions that are often transferred from generation to generation. Irrespective of these family traditions, food availability might lead to overfeeding, in its turn leading to metabolic adaptations. Apart from selection, could these adaptations to the social environment have transgenerational effects? This study will attempt to answer the following question: Can overeating during a child's slow growth period (SGP), before their prepubertal peak in growth velocity influence descendants' risk of death from cardiovascular disease and diabetes? Data were collected by following three cohorts born in 1890, 1905 and 1920 in Överkalix parish in northern Sweden up until death or 1995. The parents' or grandparents' access to food during their SGP was determined by referring to historical data on harvests and food prices, records of local community meetings and general historical facts. If food was not readily available during the father's slow growth period, then cardiovascular disease mortality of the proband was low. Diabetes mortality increased if the paternal grandfather was exposed to a surfeit of food during his slow growth period. (Odds Ratio 4.1, 95% confidence interval 1.33–12.93, *P*=0.01). Selection bias seemed to be unlikely. A nutrition-linked mechanism through the male line seems to have influenced the risk for cardiovascular and diabetes mellitus mortality.

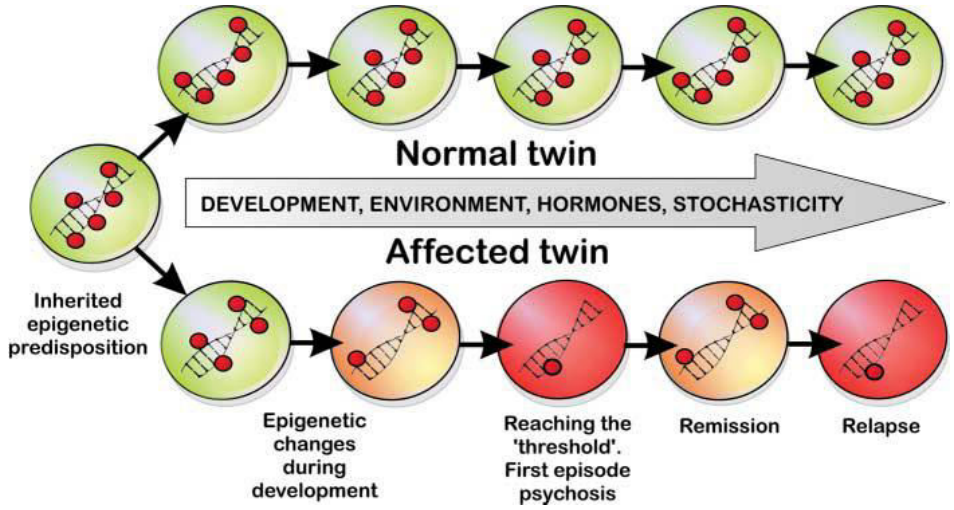
European Journal of Human Genetics (2002) **10**, 682–688. doi:10.1038/sj.ejhg.5200859

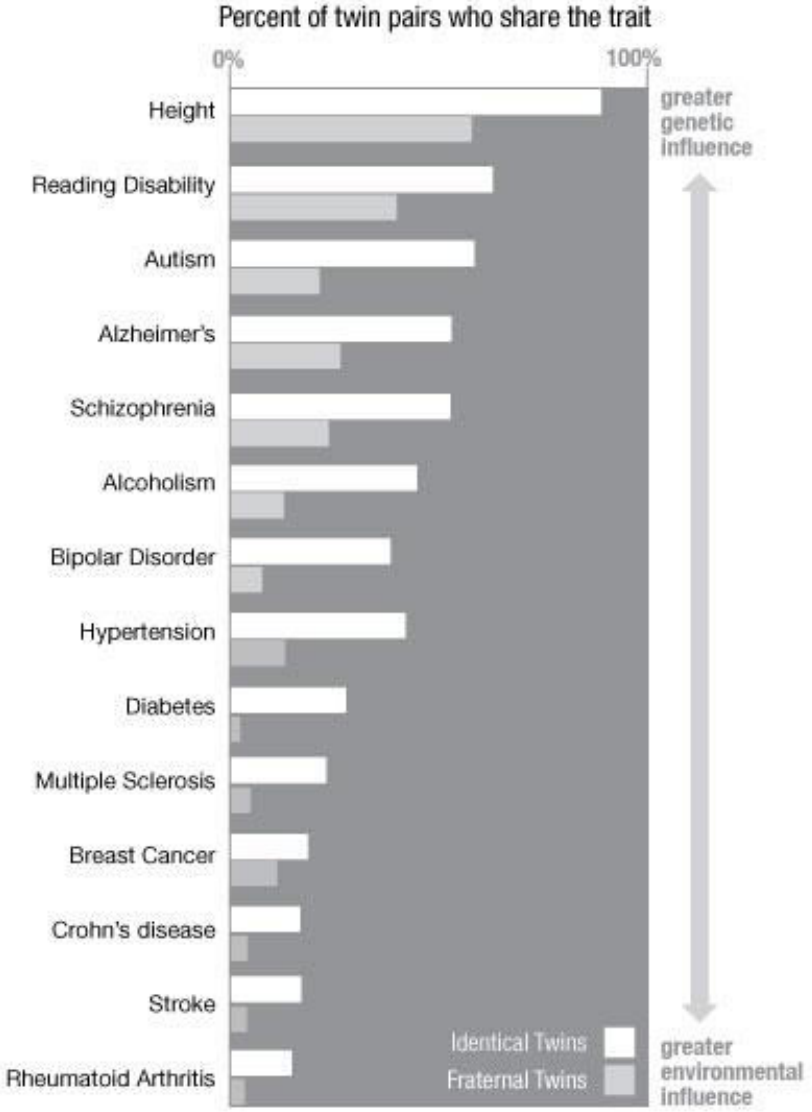
Among the sex-specific effects noted;

- a greater body mass index (BMI) at 9 years in **sons,** but not daughters, of fathers who began smoking early.
- The paternal grandfather's severe change in food supply was only linked to the cardiovascular mortality risk ratio of grandsons and **not granddaughters.**
- The paternal grandmother's food supply was only associated with the **granddaughters' cardiovascular mortality risk ratio**. It was 2 fold higher when she had a good food than poor food during the SGP.
- The father's poor food supply and the mother's good food supply during SGP were associated with a lower risk of cardiovascular death.[1]

Environmental factors influence epigenetic difference and disease susceptibility even among twins

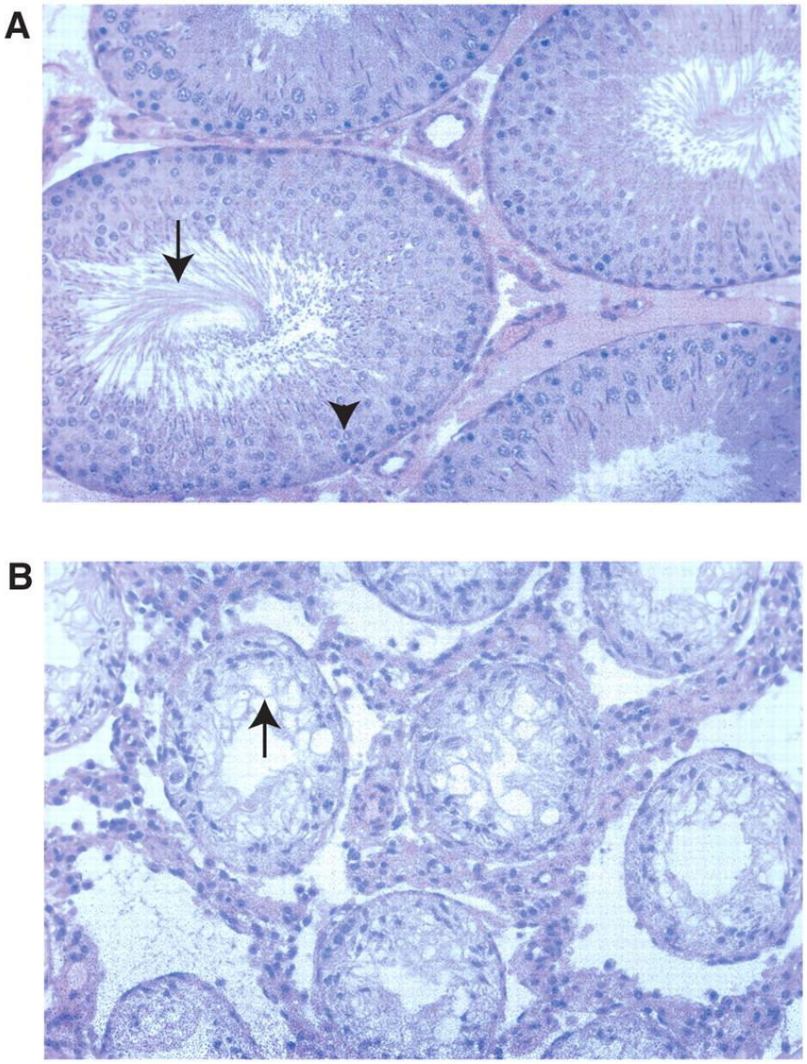


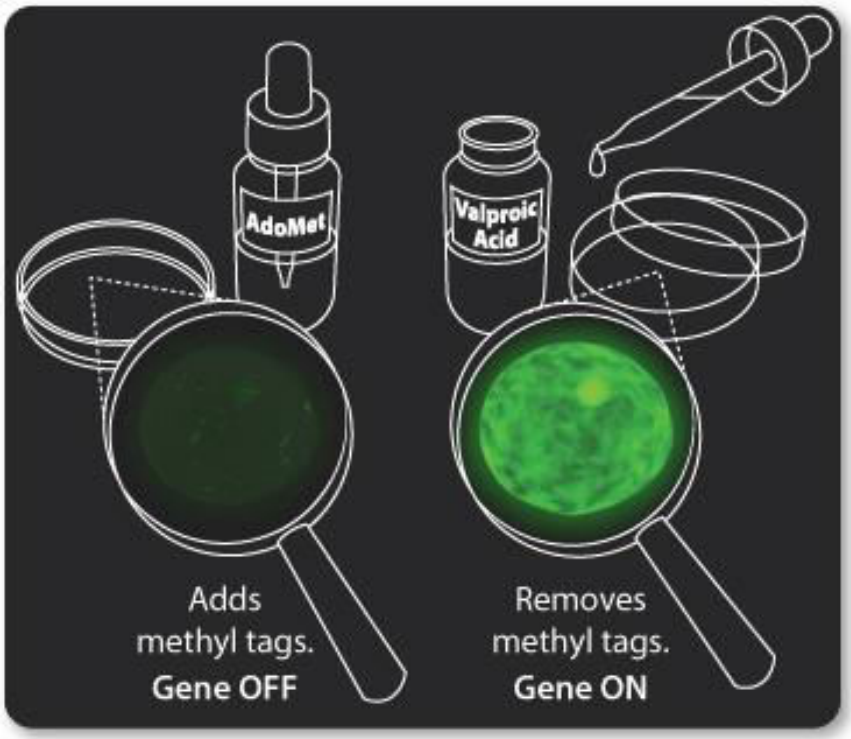




Environmental factors – vinclozolin antiandrogenic factor

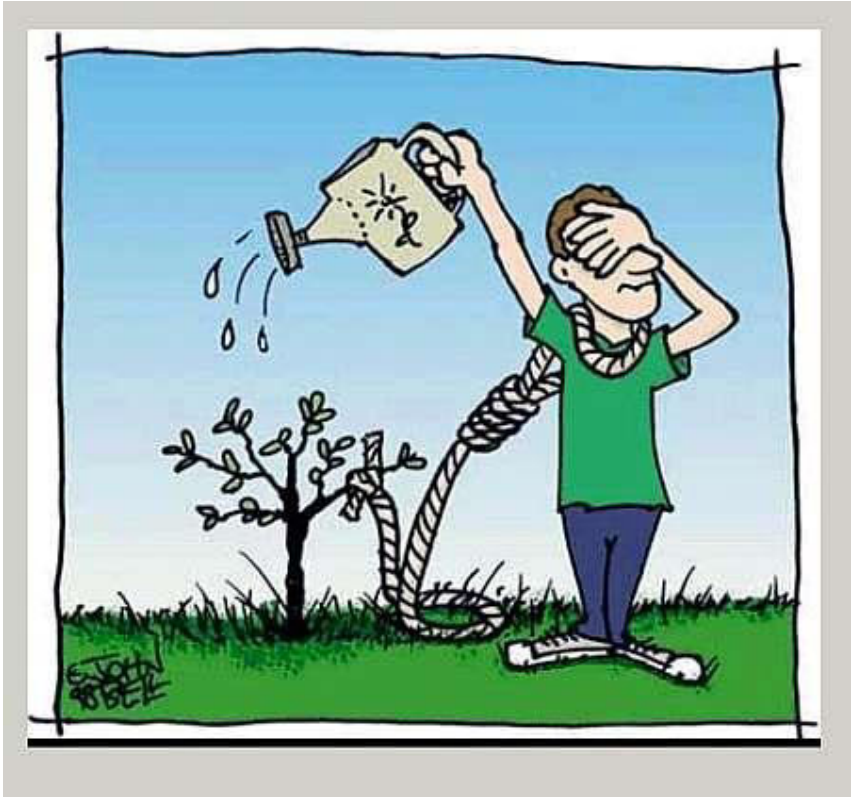
Maternal exposure

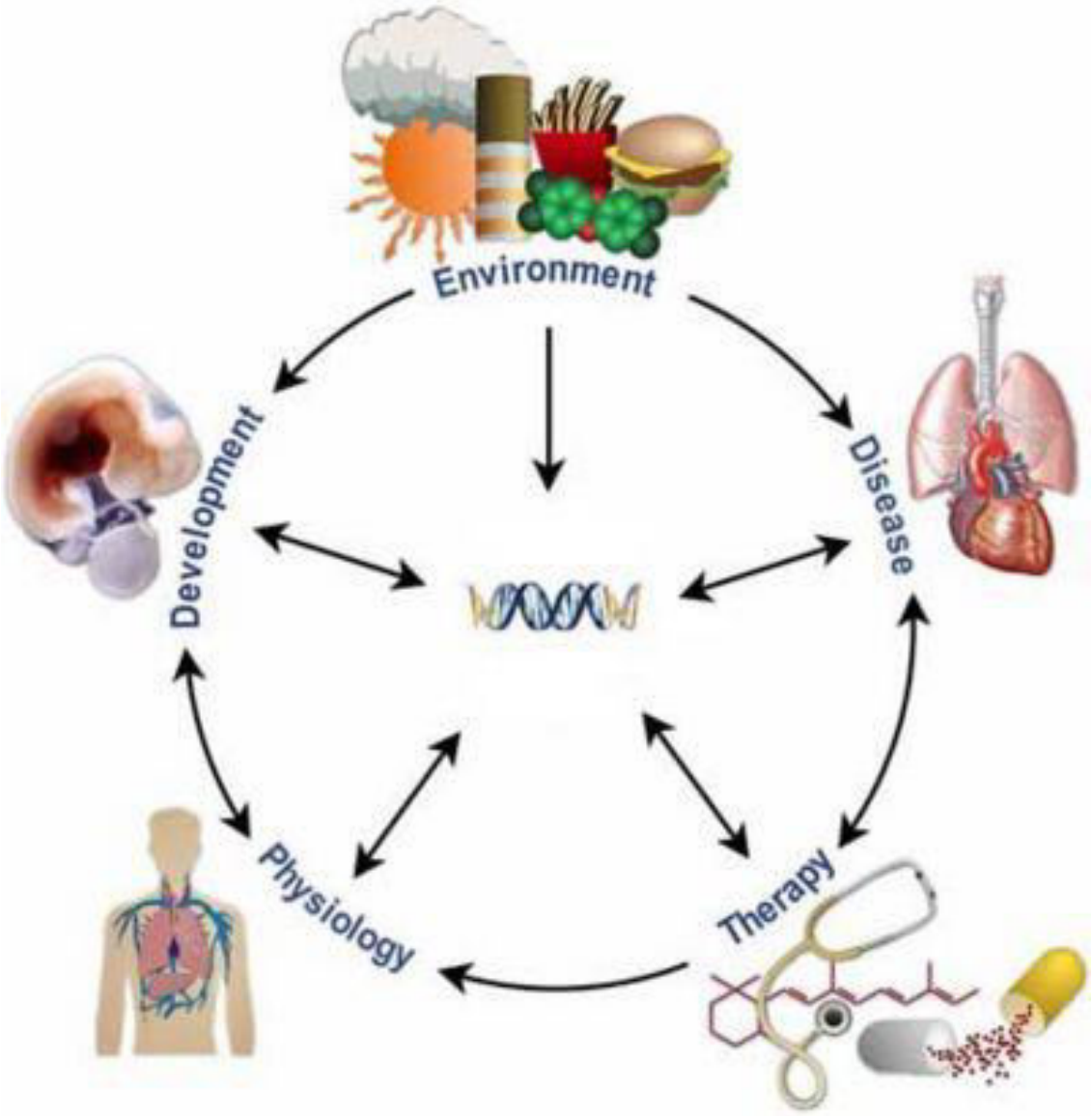




Child abuse leads to epigenetic changes – resulting in mental disorders and suicide

Child abuse and suicide – maternal care and epigenetics

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TAKE HOME MESSAGE ??


MY life
MY Rules..


Thank you