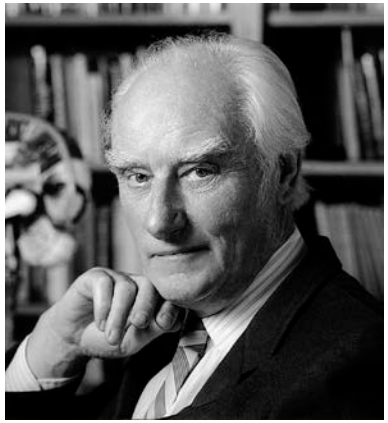
# Epigenetic concepts

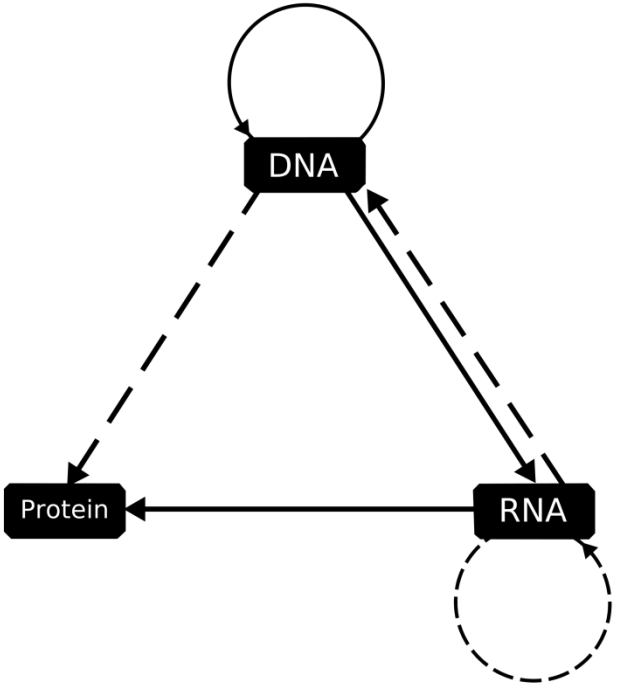
Associate professor in molecular epidemiology

Jonas Mengel-From



# The central dogma

> The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred back from protein to either protein or nucleic acid.
>
> — *Francis Crick, 1970*



# Epigenetic definition

Genetics :

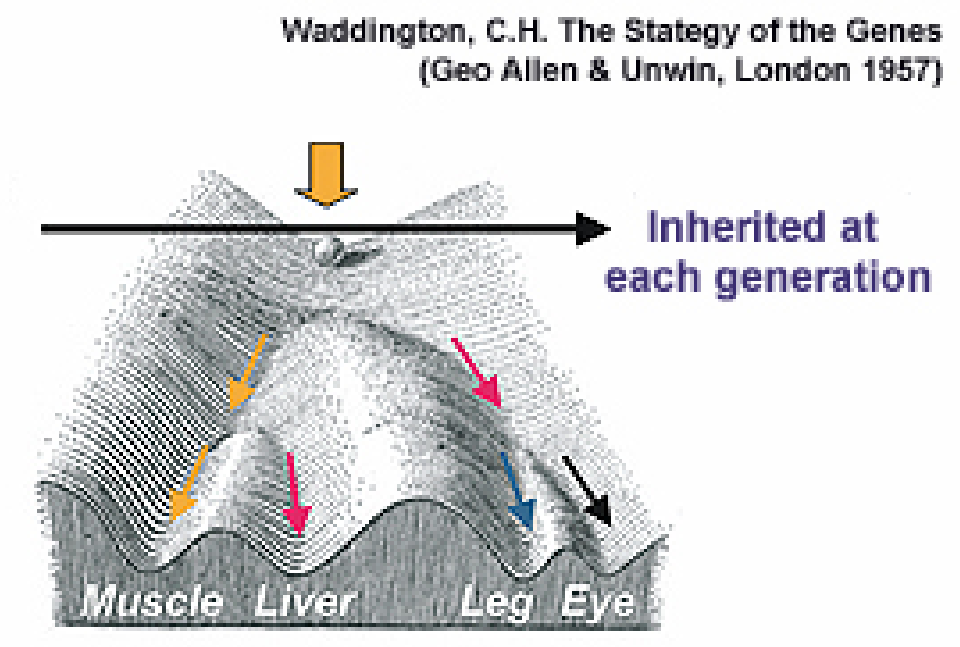
- heritable variation in the DNA sequence that is passed on from generation to generations.

Epigenetics,

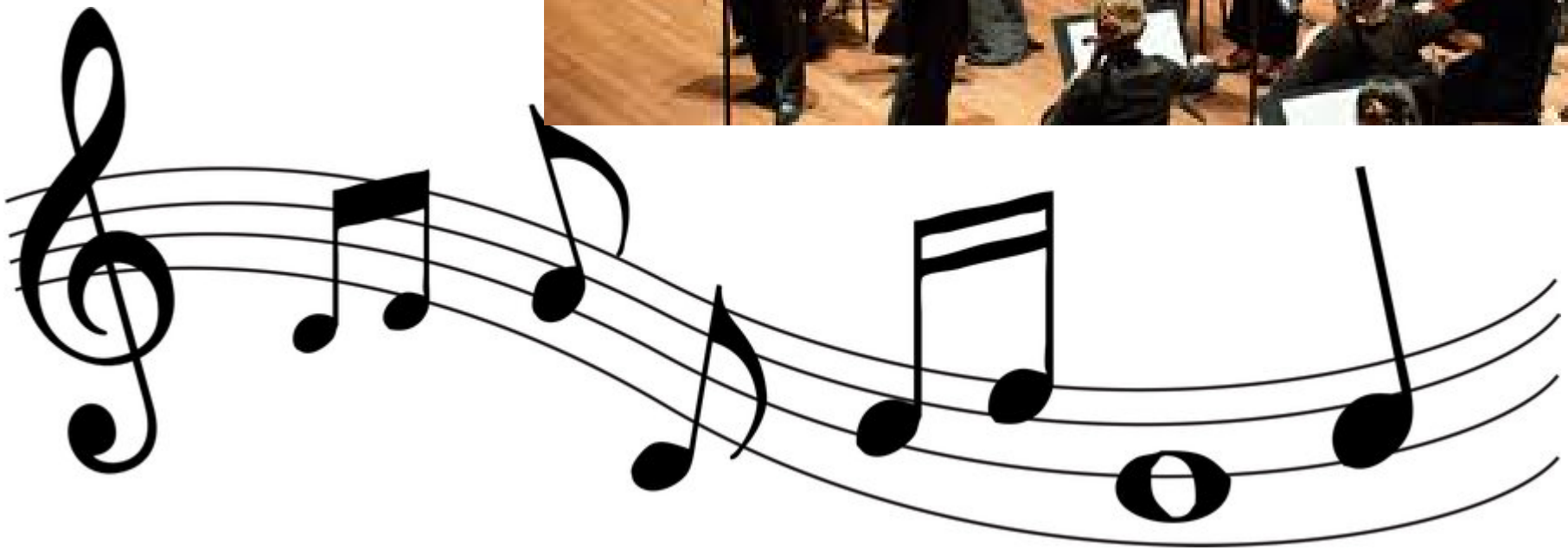
- In Greek Epi = over/on/at

**“heritable variation that does not change the DNA sequence”**

# Epigenetics during development

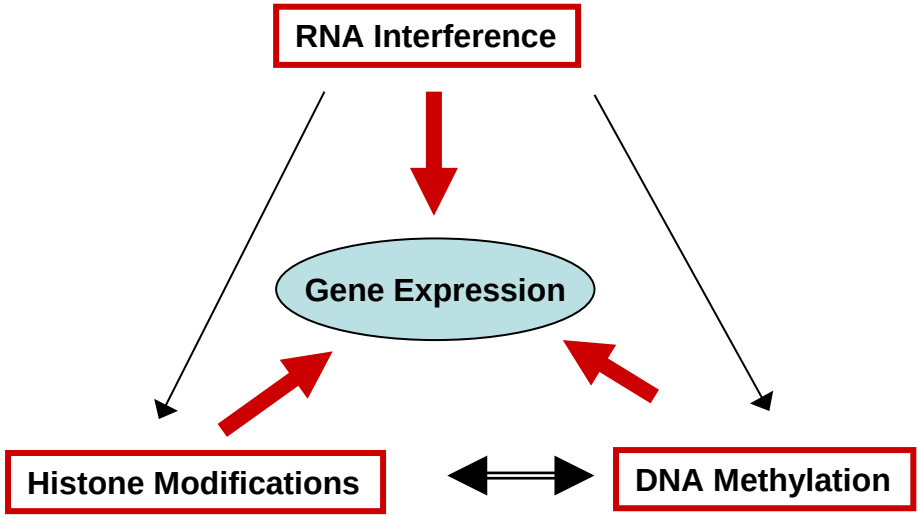


# Epigenetics



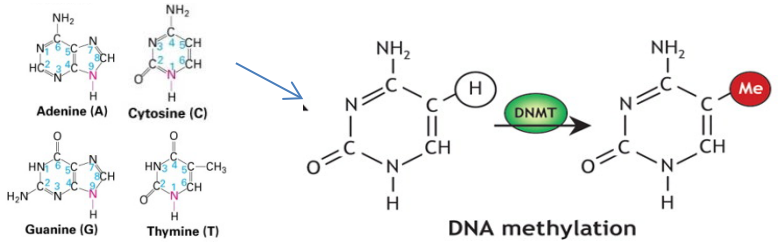
# Epigenetic elements

- Elements of (heritable) variation in the genome that does not change the DNA sequence
  - DNA methylation
  - Histone modification
  - miRNA (regulation)
- Involved in the activity of genes and gene expression

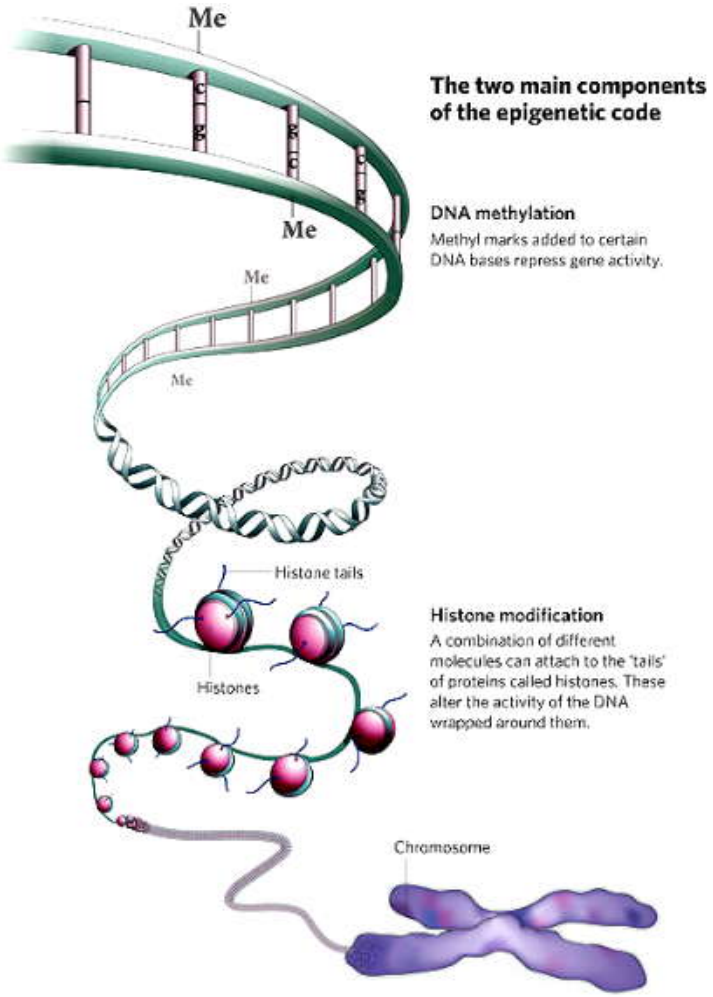


# DNA Methylation

- The DNA can be chemically altered (C5 position on the cytosine). $CH_3$-metylation is added to the CpG islands by a enzymatic process (methyltransferases)

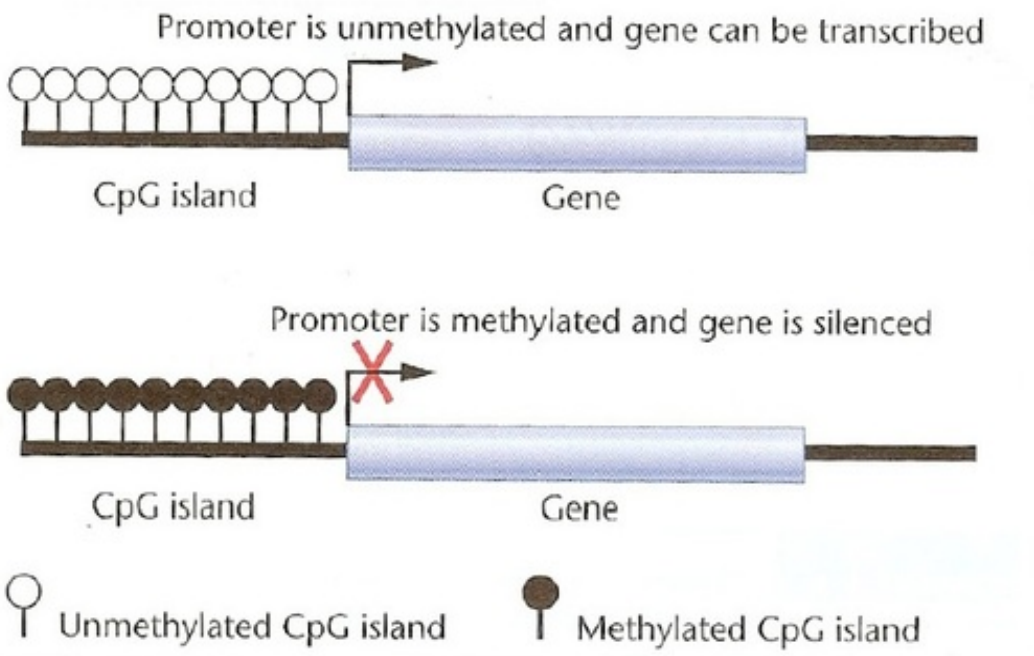



- The DNA is wrapped around proteins (Histones). Also the histones can be altered by e,g. methylation, acetylation

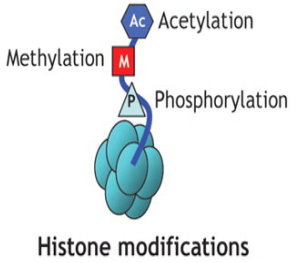


# Epigenetics gene regulation

- DNA methylation is associated with inactive genes

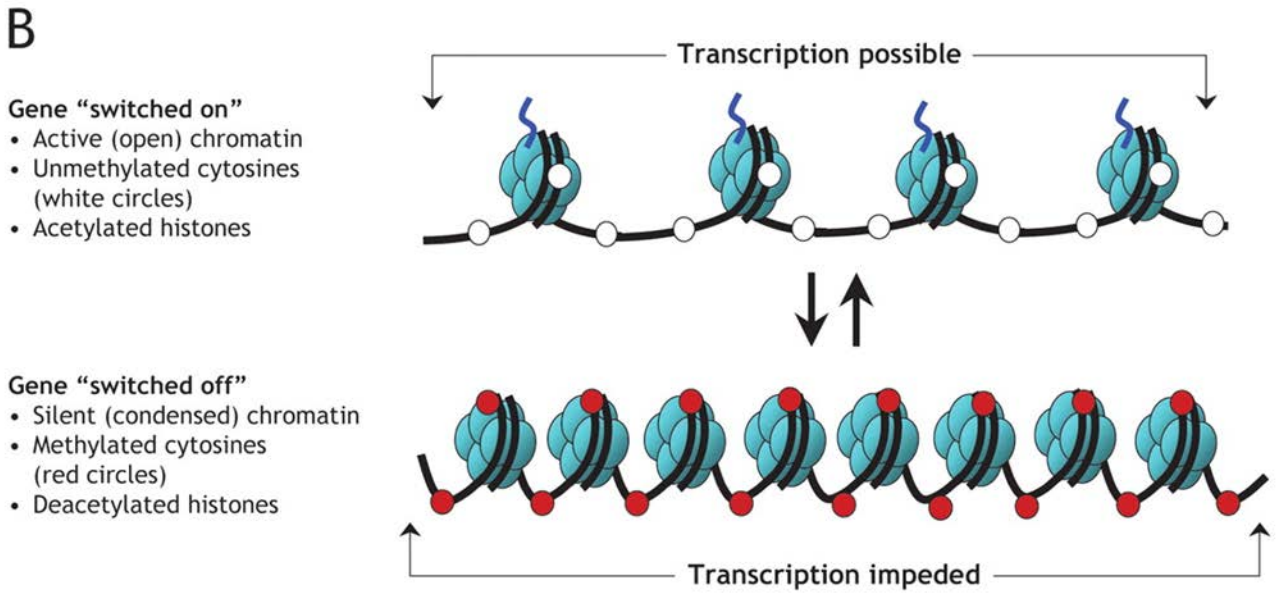


# Histone modifications



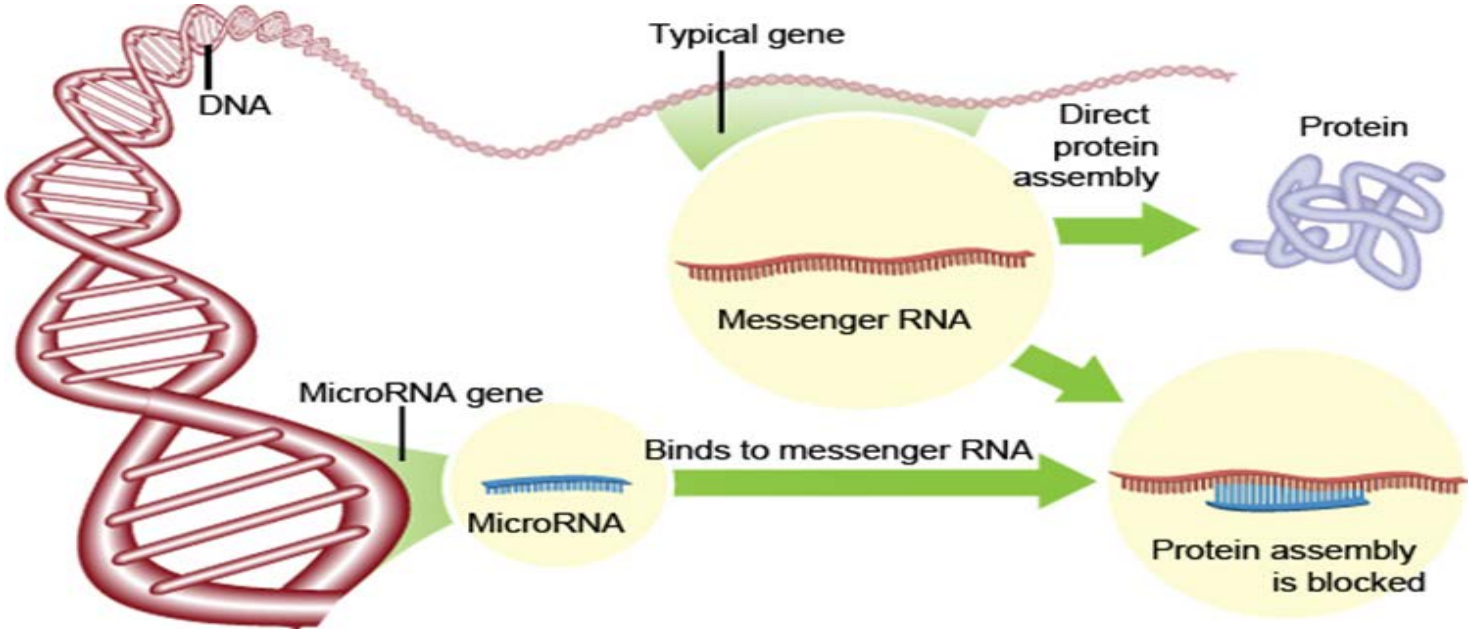
Histone modifications

- There are several types of histone modifications ; acetylation, methylation, phosphorylation, ribosylation etc.
- Histone acetylation is associated with gene activity



# Epigenetics

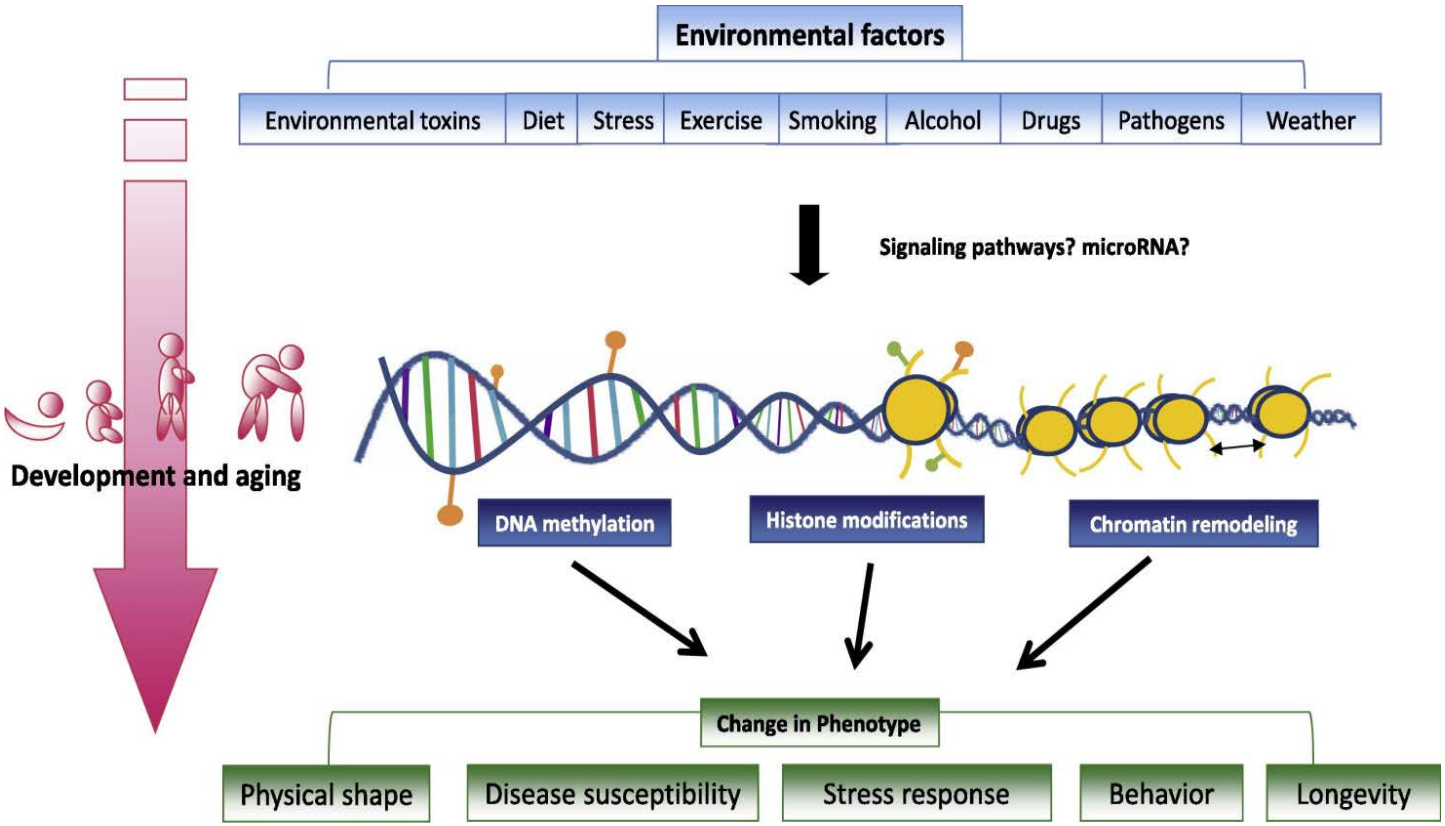
- Non-coding RNA
  - miRNA: small interfering RNAs (20-22 nucleotides) regulates synthesis of proteins



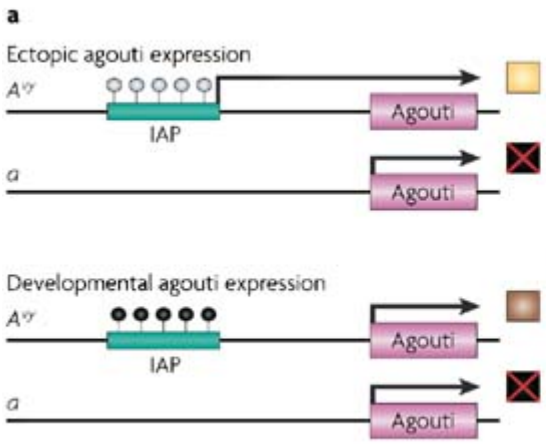
# Epigenetic theoretical concept

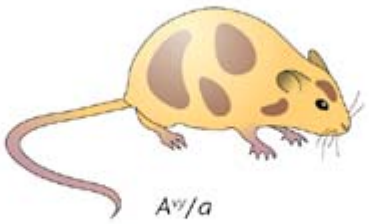
The French biologist Jean-Baptiste Lamarck (1744–1829) recorded in his work on the evolutionary theory that the sons of a blacksmith have larger arm muscles than the sons of weavers.

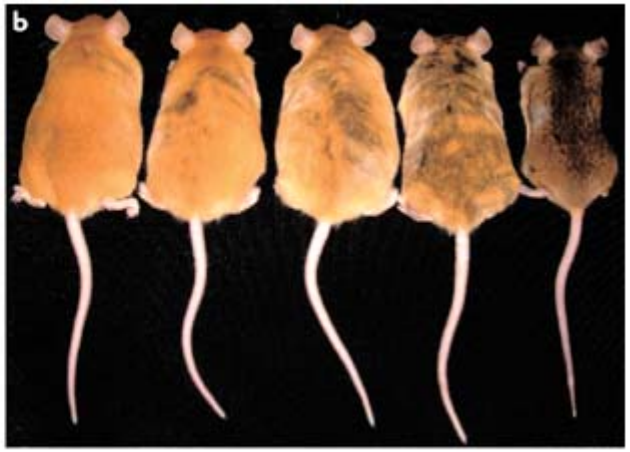
# Environment lifestyle and Epigenetics



# Diet and the Agouti Mouse model



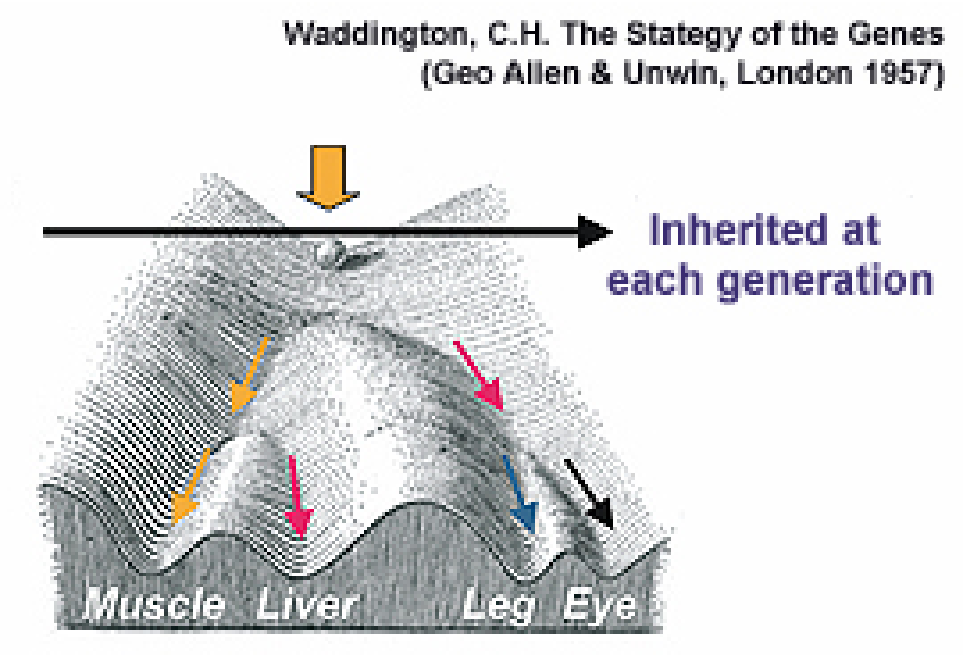




Nature Reviews | Genetics

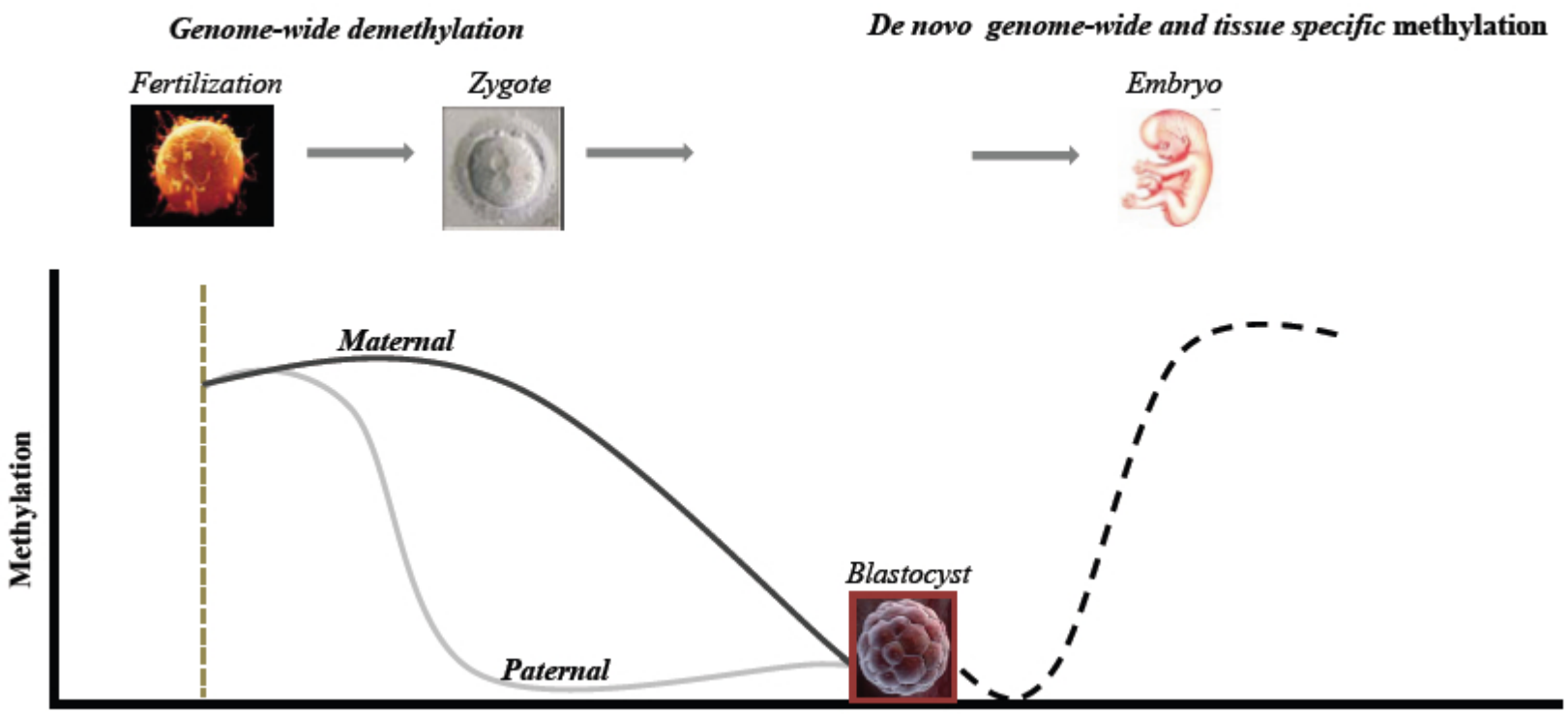
# Dutch Famine of 1944-1945

# Transgenerational inheritance

# Epigenetics during development



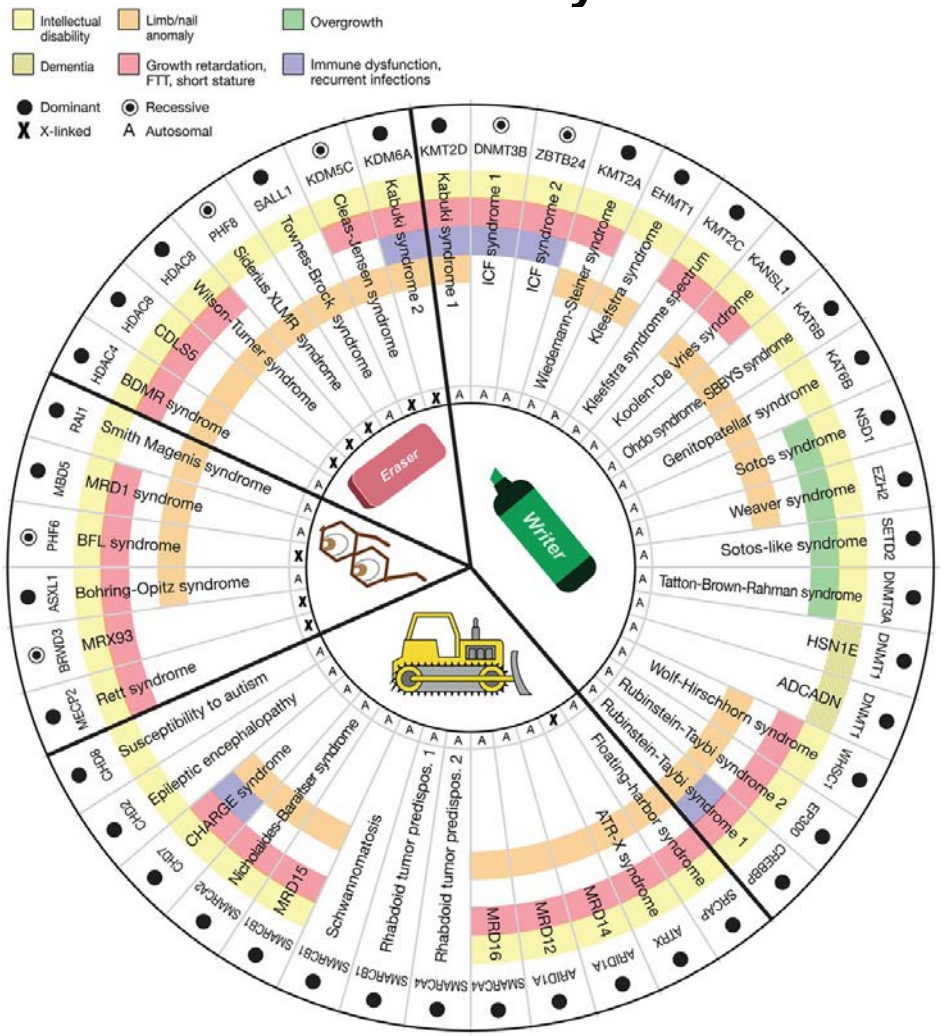
# De-programing and reactivation of the Epigenome



# Genes in the Epigenetic machinery

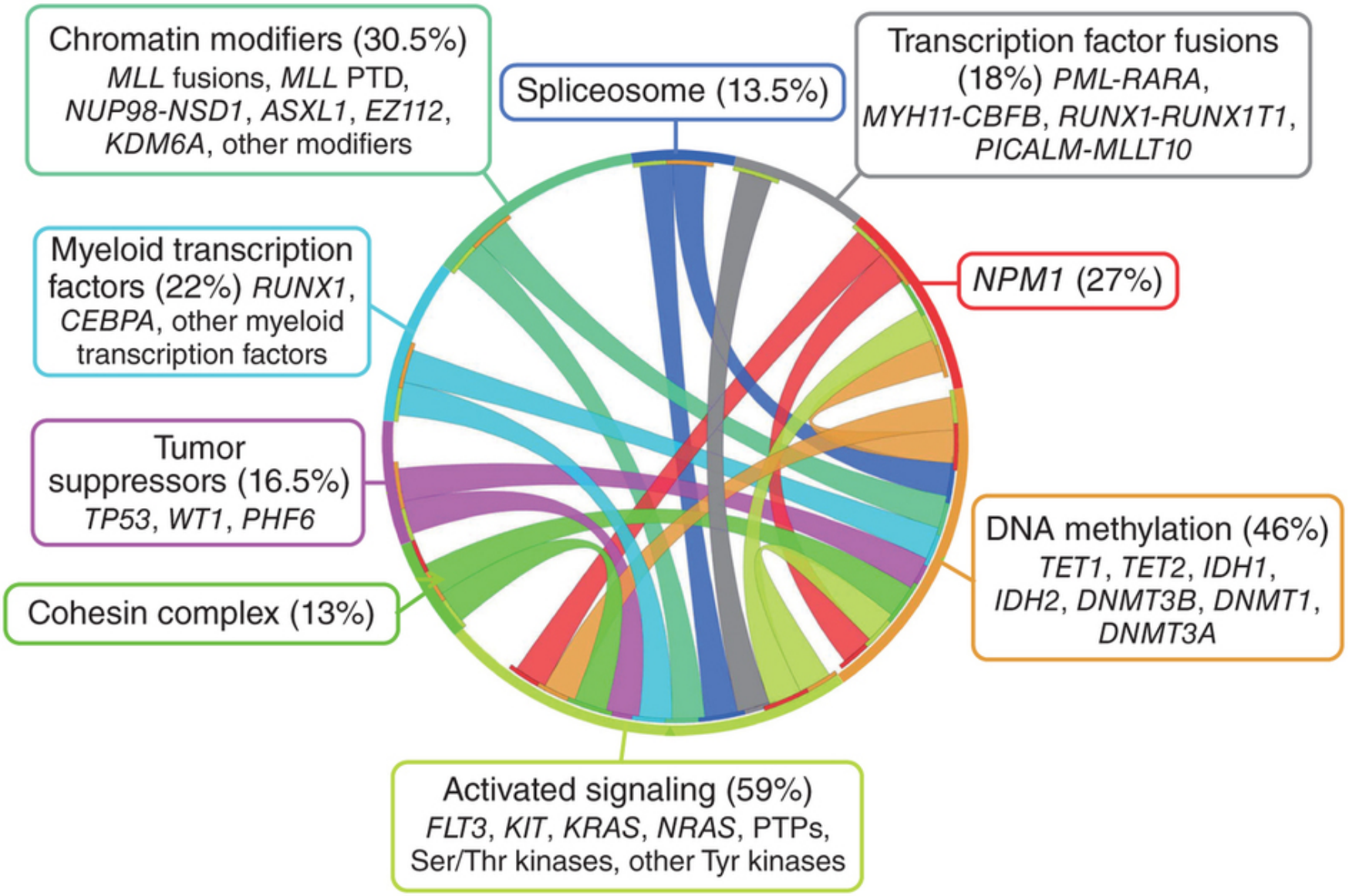
- **Writers**: enzymes that adds epigenetic modifications, DNA Methyltransferases
- **Readers**: enzymes that recognize epigenetic modifications, can contain methyl-binding domains (MBDs)
- **Erasers**: enzymes that removes epigenetic modifications through formation of (5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine)
- **Remodelers**: Enzymes that assist process to facilitate access of nucleosomal DNA by remodeling the structure, composition and positioning of nucleosomes

# Characteristic features of the Mendelian disorders of the epigenetic machinery.



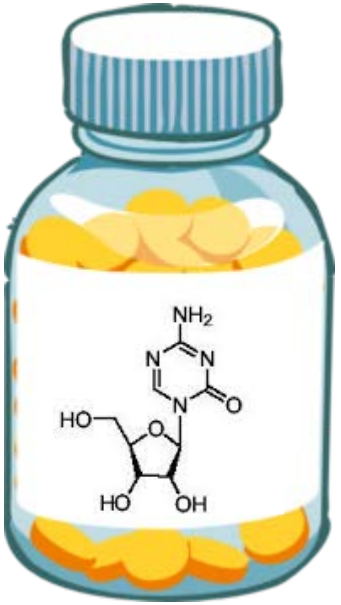

Hans Tomas Bjornsson Genome Res. 2015;25:1473-1481

# Somatic genetics in Acute Amyloid Leukemia




**A panoramic view of acute myeloid leukemia** Sai-Juan Chen,[1] Yang Shen[1] & Zhu Chen[1] Affiliations Corresponding author Journal name:Nature Genetics Volume: 45, Pages:586–587 Year published:(2013) DOI:doi:10.1038/ng.2651

# Treatment - 5-azacytidin




- In 1970's Dr. Peter Jones showed 5-azacytidin could alter the Epigenetics (cell type)
- 5-azacytidin was later shown to inhibit the global DNA methylation (Writers)
- Since 2009 5-azacytidin (Vidaza) has been used for treating AML (leukemia)
- Other epigenetic treatments are e.g. Histone acetylation inhibitors (Entinostat)

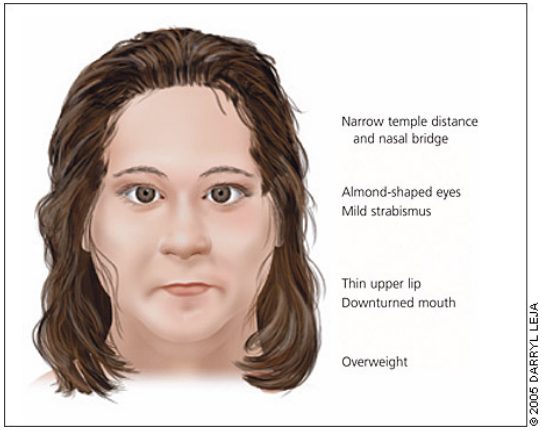
# Imprinting

# Imprinting

For some inherited diseases/traits it is important if genes are inherited from the mother or the farther.

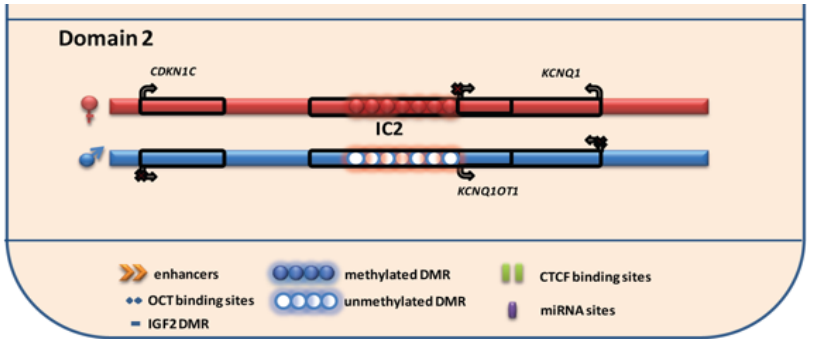
…e.g. if a mutation on chromosome 15 is on the paternal chromosome it causes Prader-Willi's syndrome

and on the maternal chromosome it causes Angelman's syndrome




# DNA methylation and imprinting

- About 50 human imprinted genes are known
- The reason for this is that some genes when inherited  from the father is methylated while the gene from the mother is no, or versa visa
- E.g. Beckwith-Wiedemanns syndrome

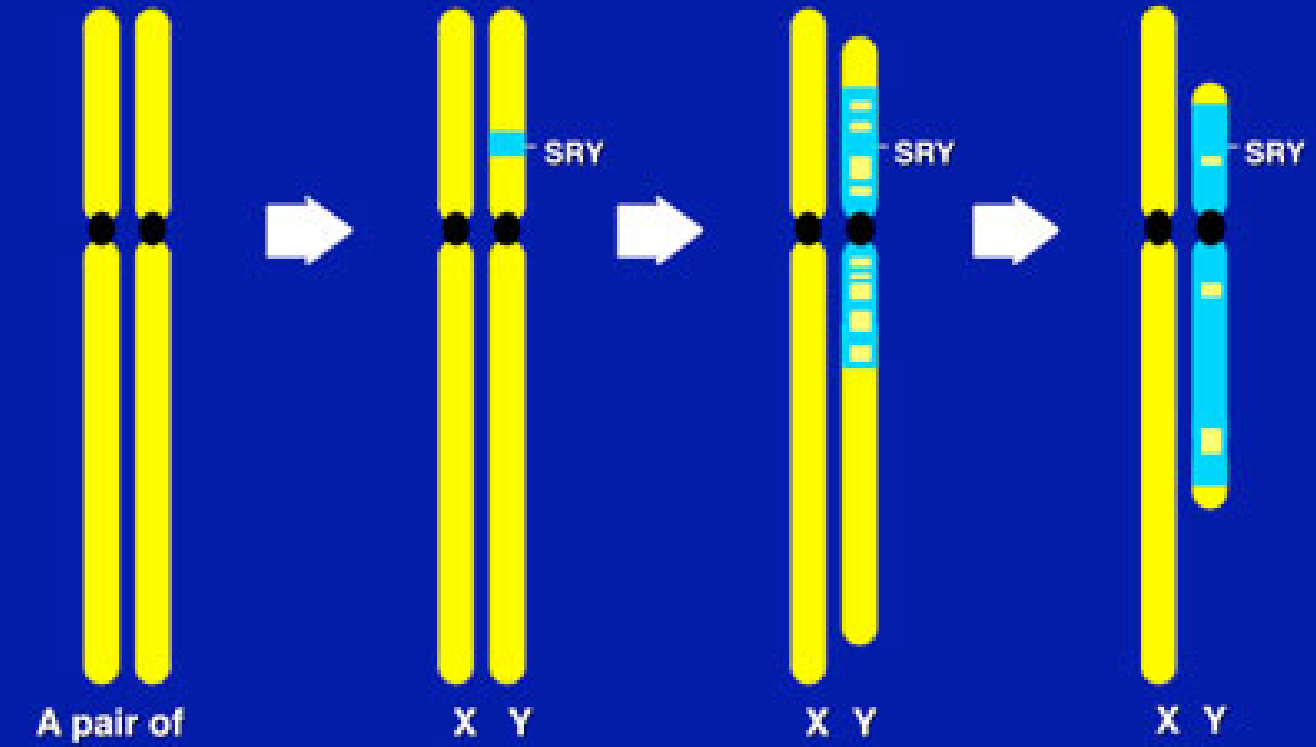



Shoufani et al., Am J Med Genet C Semin Med Genet. 2013 May;163(2):131-40

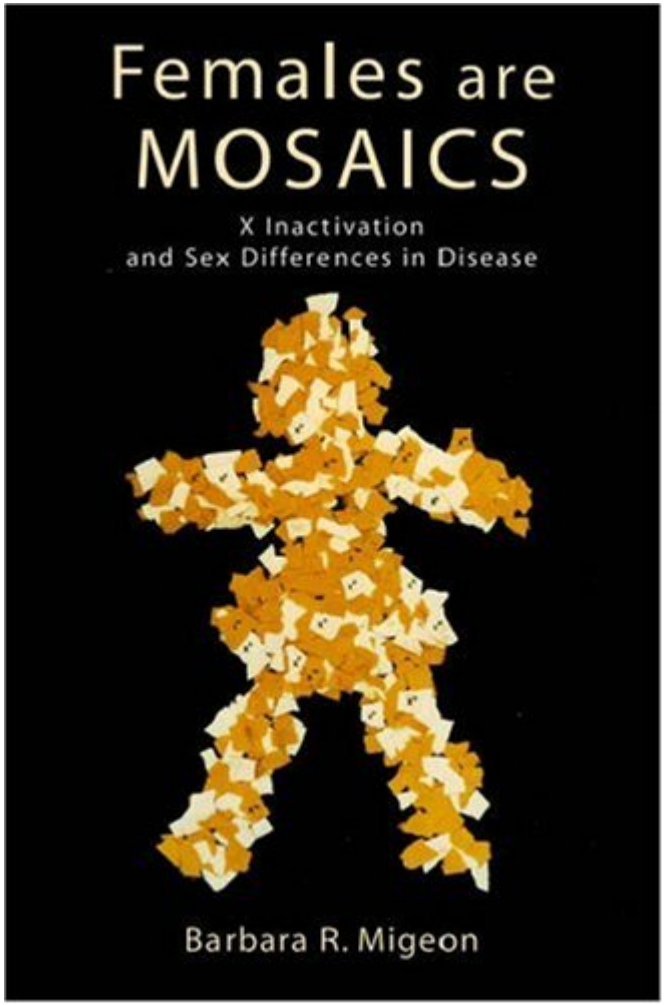
# Men and Women

- women live on average longer than men
- What genetic differences are there between man and women?

# Classical Model of Sex Chromosome Evolution: Y as Decayed X



# X chromosome inactivation
# "*Lyonization*"



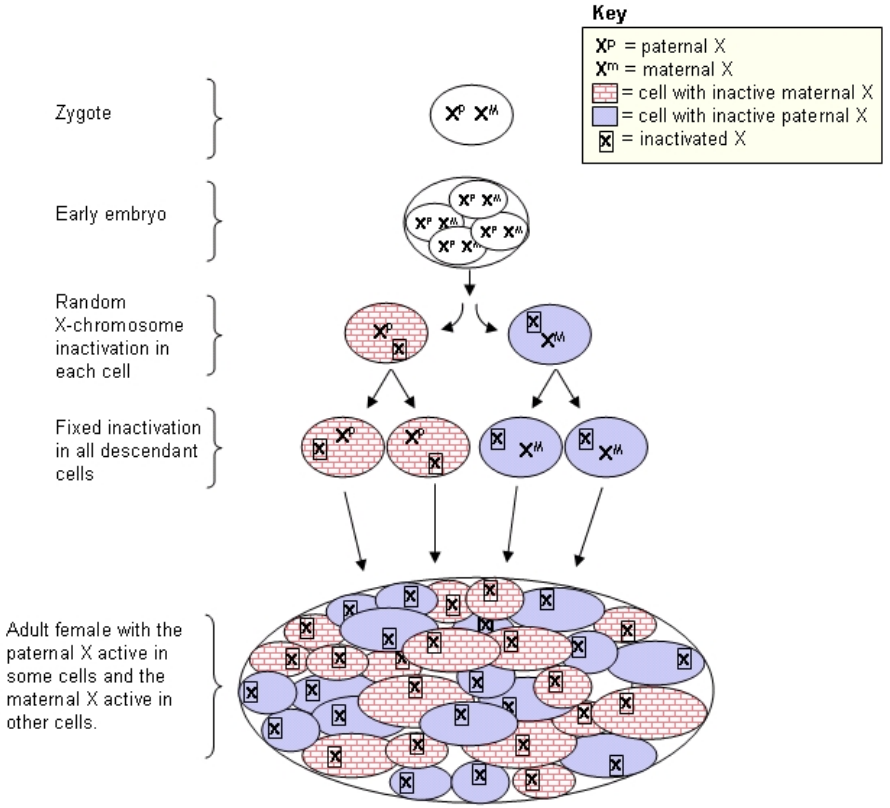




Illustration adapted from Thompson & Thompson Genetics in Medicine, 6th Edition; RL Nussbaum, RR McInnes, HF Willard, *Patterns of Single-Gene Inheritance*, Figure 5-16, pg 67, Copyright 2001, with permission from Elsevier.

# Skewed X-inactivation and survival

| Degree of skewing | | Adjusted for age | | | Adjusted for age, cognitive and physical abilities | | |
|---|---|---|---|---|---|---|---|
| | Min. - Max. Value | HR* | 95% CI | p-value | HR* | 95% CI | p-value |
| First Quartile | 50 – 63 | 1 | - | - | 1 | - | - |
| Second Quartile | 64 -74 | 0.67 | 0.50 – 0.92 | 0.012 | 0.67 | 0.48 – 0.93 | 0.016 |
| Third Quartile | 75 - 87 | 0.87 | 0.66 – 1.13 | 0.29 | 0.81 | 0.63 – 1.05 | 0.11 |
| Fourth Quartile | 88 – >95 | 0.77 | 0.58 – 1.02 | 0.065 | 0.74 | 0.56 – 0.98 | 0.036 |

"On the individual level (IL) there is evidence that skewed X-inactivation favors survival."

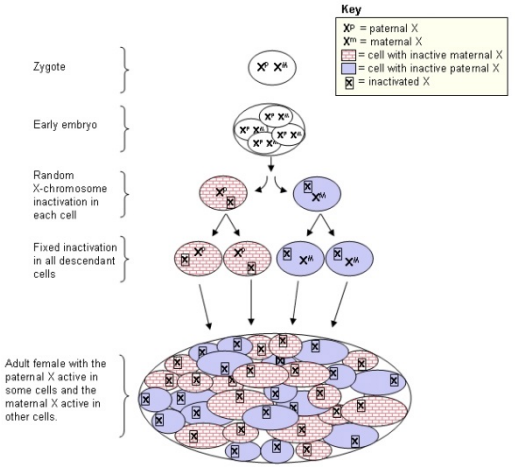
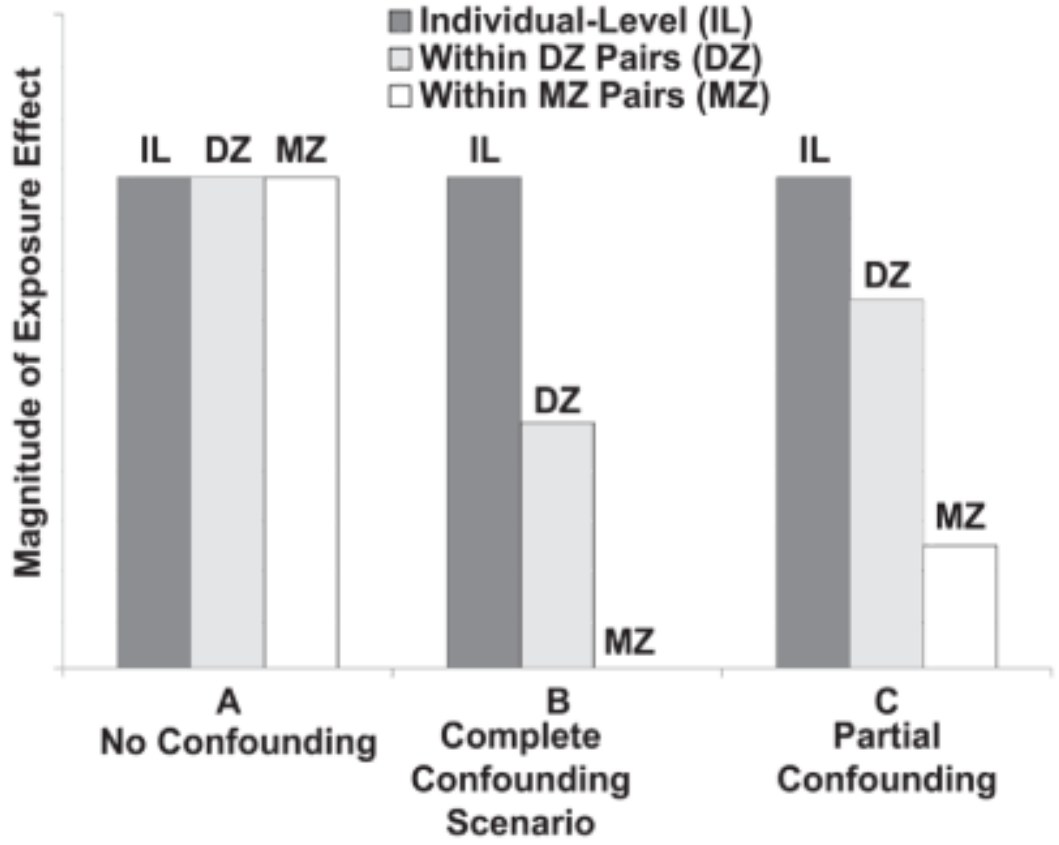



Illustration adapted from Thompson & Thompson Genetics in Medicine, 6th Edition; RL Nussbaum, RR McInnes, HF Willard, *Patterns of Single-Gene Inheritance*, Figure 5-16, pg 67, Copyright 2001, with permission from Elsevier.

Mengel-From J, Thinggaard M, Christiansen L, Vaupel JW, Orstavik KH, Christensen K.. Eur J Hum Genet. 2012 Mar;20(3):361-4. doi: 10.1038/ejhg.2011.215. Epub 2011 Dec 7.

# Causal effects

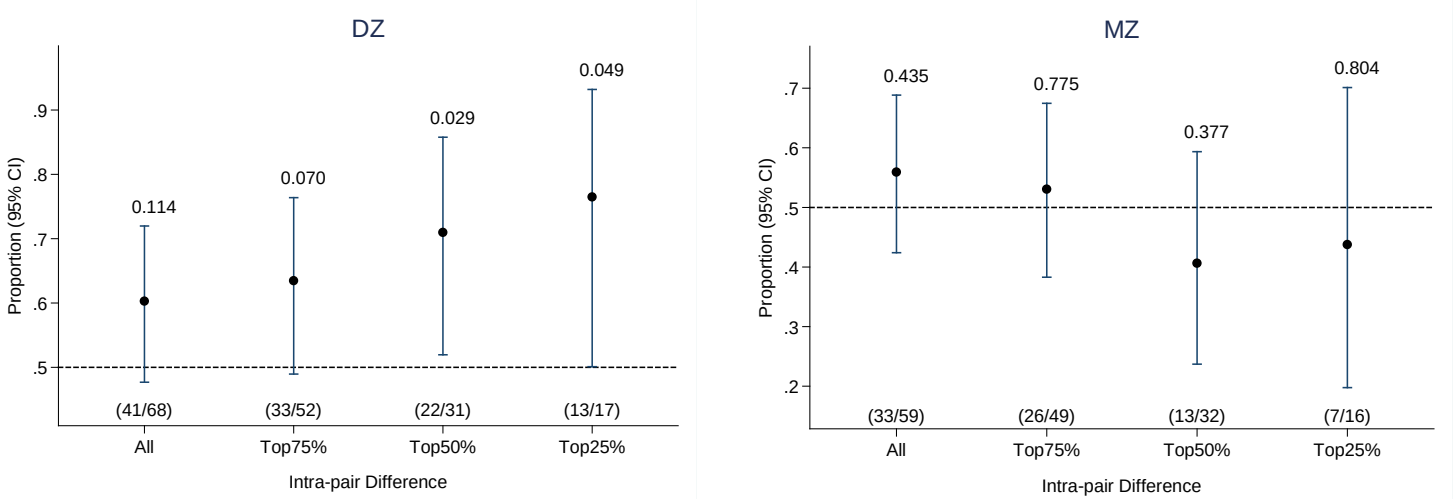



McGue M, Osler M, Christensen K. Causal Inference and Observational Research: The Utility of Twins. Perspect Psychol Sci. 2010 Sep;5(5):546-56.

# Within MZ and DZ pairs

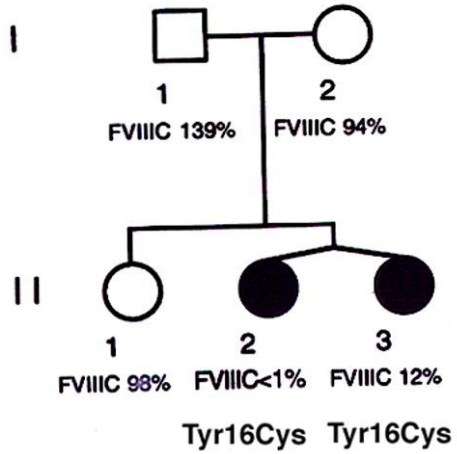
- Does the twin with the highest degree of skewed X-inactivation (DS) live longer than the co-twin?

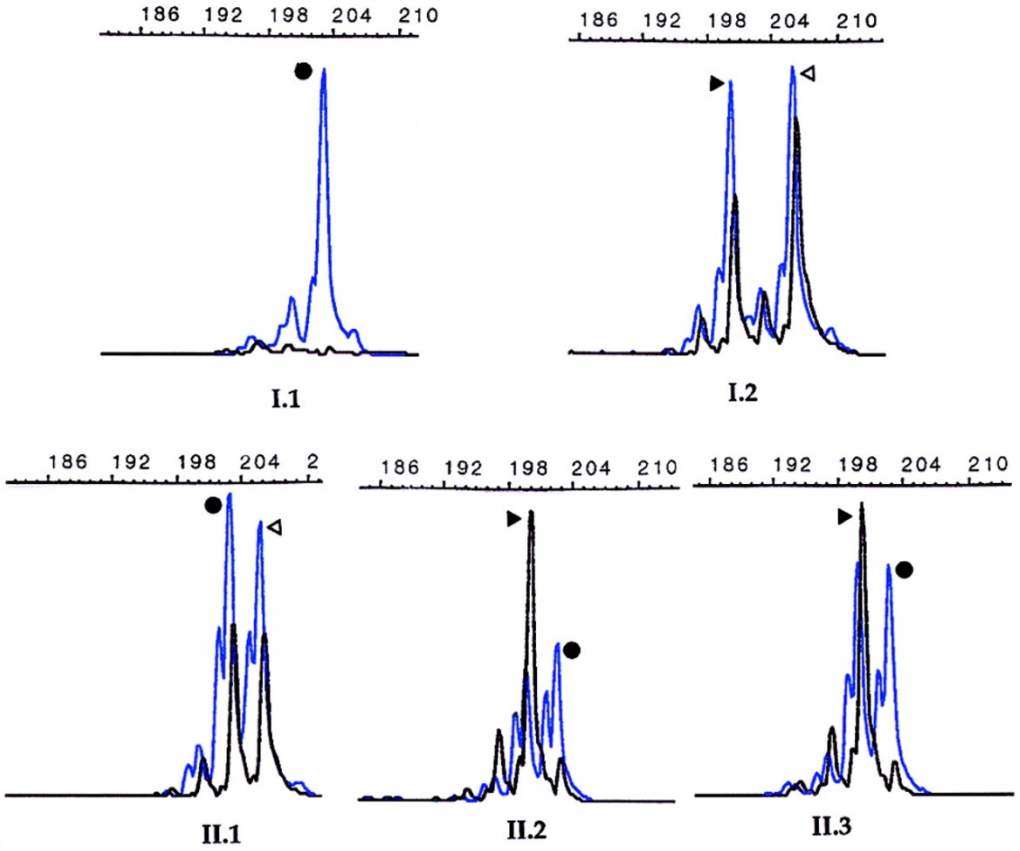
$$Pr(Survival_{Twin1} > Survival_{Twin2} \mid DS_{Twin1} > DS_{Twin2}) > ½$$




Mengel-From J, Thinggaard M, Christiansen L, Vaupel JW, Orstavik KH, Christensen K. Skewed X inactivation and survival: a 13-year follow-up study of elderly twins and singletons. Eur J Hum Genet. 2012 Mar;20(3):361-4. doi: 10.1038/ejhg.2011.215. Epub 2011 Dec 7.

# Monozygotic twins both with Hemophilia A




Valleix S et al. Blood 2002;100:3034-3036. (Hemophilia A)

Journal of Alzheimer's Disease 63 (2018) 591–601
DOI 10.3233/JAD-171163
IOS Press



# Circulating, Cell-Free Micro-RNA Profiles Reflect Discordant Development of Dementia in Monozygotic Twins

Jonas Mengel-From[a,b,*], Mette E. Rønne[c], Anting L. Carlsen[c], Kristin Skogstrand[c], Lisbeth A. Larsen[a], Qihua Tan[a,b], Lene Christiansen[a], Kaare Christensen[a,b,d] and Niels H.H. Heegaard[c,d]

[a]*Department of Public Health, The Danish Aging Research Center and The Danish Twin Registry, Epidemiology, Biostatistics and Biodemography Unit, University of Southern Denmark, Odense, Denmark*
[b]*Department of Clinical Genetics, Odense University Hospital, Odense, Denmark*
[c]*Department of Autoimmunology and Biomarkers, Statens Serum Institut, Copenhagen, Denmark*
[d]*Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark*
[e]*Department of Congenital Disorders, Center for Neonatal Screening, Statens Serum Institut, Copenhagen, Denmark*

Accepted 14 February 2018

**Abstract**. We aim to examine if circulating micro-RNA and cytokine levels associate with dementia diagnosis and cognitive scores. To test our hypothesis, we use plasma donated from 48 monozygotic twin pairs in 1997 and 46 micro-RNAs and 10 cytokines were quantified using microfluidic RT-qPCR and multiplex solid-phase immunoassays, respectively. Micro-RNA and cytokine profiling were examined for associations with dementia diagnoses in a longitudinal registry study or with cognitive scores at baseline. Thirty-six micro-RNAs and all cytokines were detected consistently. Micro-RNA profiles associate with diagnoses and cognitive scores at statistically significant levels while cytokine only showed trends pointing at chronic inflammation in twins having or developing dementia. The most notable findings were decreased miR-106a and miR-210, and increased miR-106b expression in twins with a dementia diagnosis. This pioneering evaluation of micro-RNA and cytokine and dementia diagnosis suggests micro-RNA targets in vasculogenesis, lipoprotein transport, and amyloid precursor protein genes.

| miRNA | Dementia Discordant twins | | | Discordance in quantitative difference in CCS in twins without dementia | | |
|---|---|---|---|---|---|---|
| | No. twin pairs | β0 coefficient | p-value | No. twin pairs | β1 coefficient | p-value |
| hsa-let-7b-5p | 22 | -0.27 | 0.71 | 20 | 0.03 | 0.78 |
| hsa-let-7f-5p | 5 | 1.51 | 0.75 | 1 | - | - |
| hsa-let-7i-5p | 16 | 2.13 | 0.42 | 14 | 0.22 | 0.34 |
| hsa-miR-101-3p | 22 | -0.10 | 0.94 | 20 | -0.07 | 0.78 |
| hsa-miR-106a-5p | 22 | -1.41 | 0.10 | 20 | 0.01 | 0.97 |
| ***hsa-miR-106b-5p*** | ***22*** | ***3.16[a]*** | ***0.03[a]*** | 20 | -0.01 | 0.98 |
| hsa-miR-128-3p | 7 | -2.14[b] | 0.33[b] | 9 | 0.55 | 0.45 |
| hsa-miR-130b-3p | 18 | -0.06 | 0.98 | 19 | -0.05 | 0.74 |
| hsa-miR-132-3p | 21 | *-3.50* | *0.26* | 20 | 0.35 | 0.07 |
| hsa-miR-134-5p | 15 | -0.19 | 0.96 | 15 | 0.10 | 0.84 |
| hsa-miR-142-3p | 22 | 0.70 | 0.46 | 20 | 0.02 | 0.91 |
| hsa-miR-145-5p | 14 | 5.96 | 0.18 | 15 | 0.39 | 0.12 |
| hsa-miR-146a-5p | 22 | 0.22 | 0.85 | 20 | -0.02 | 0.82 |
| **hsa-miR-146b-5p** | ***22*** | ***-1.87*** | ***0.05*** | 20 | -0.13 | 0.51 |
| hsa-miR-155-5p | 22 | -2.01 | 0.22 | 20 | 0.04 | 0.83 |
| hsa-miR-15a-5p | 1 | - | - | 2 | - | - |
| hsa-miR-15b-5p | 21 | -2.61 | 0.18 | 20 | -0.03 | 0.84 |
| hsa-miR-16-5p | 22 | -0.81 | 0.39 | 20 | 0.05 | 0.72 |
| hsa-miR-17-5p | 22 | -0.49 | 0.51 | 20 | 0.01 | 0.89 |
| hsa-miR-191-5p | 22 | 1.38 | 0.18 | 20 | 0.15 | 0.20 |
| hsa-miR-20a-5p | 22 | -0.18 | 0.80 | 20 | 0.08 | 0.39 |
| **hsa-miR-210-3p** | 9 | 0.11[b] | 0.77[b] | ***14*** | ***1.19*** | ***0.02*** |
| hsa-miR-223-3p | 22 | -0.02 | 0.97 | 20 | 0.01 | 0.80 |

# Suggestive literature