Az ikerkutatások eredményeinek felhasználhatósága a prevencióban. Genetika és epigenetika a telomér kutatásban, immunoepigenetika.

Melicher Dóra

Ikerkutatás, epigenetika és radiogenomika

PhD kurzus 2015/16
9-10. óra
2016.03.01.

Physical activity, fitness, glucose homeostasis, and brain morphology in twins

- 10 fiatal felnőtt MZ ikerpár
- az utóbbi 3 évben megváltozott fizikai aktivitás

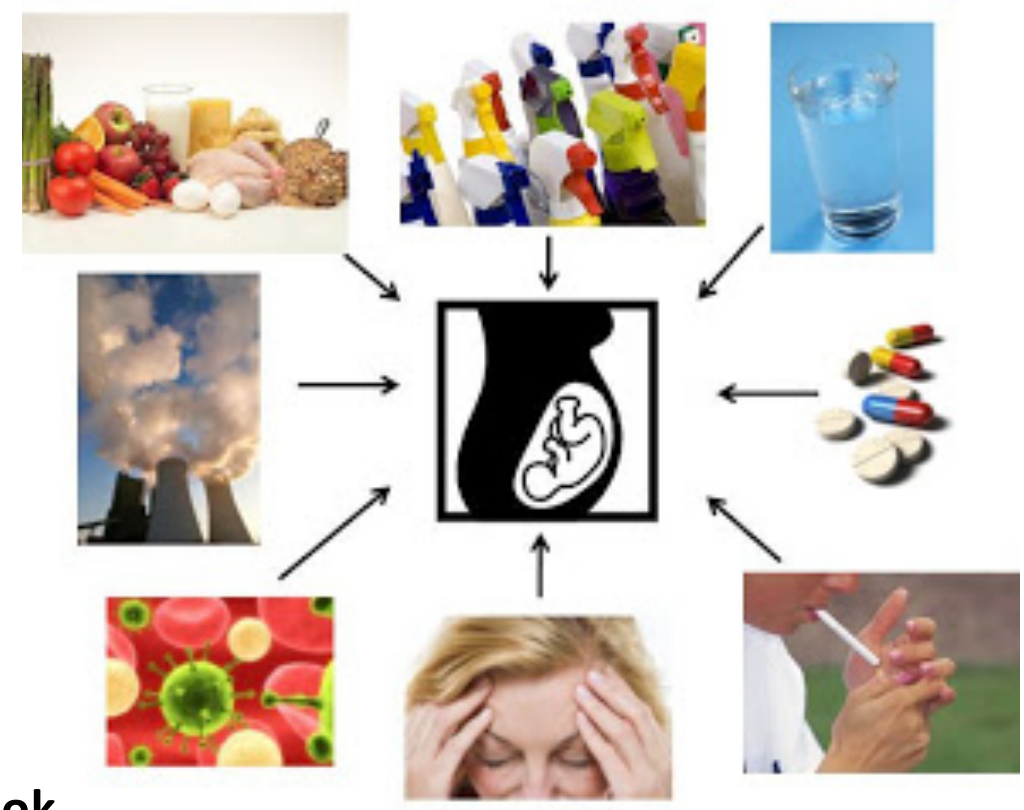
Inaktívabb iker tagok eredményei:

- **alacsonyabb állóképesség**
- **magasabb testzsír százalék**
- **inzulin rezisztencia jelei**
- **kezdődő anyagcsere problémák**

Physical activity,, fitness, glucose homeostasis, and brain morphology in twinsRottensteiner et al..,Med Sci Sports Exerc. 2015 Mar;47(3):509-18

Epigenetikai hatások

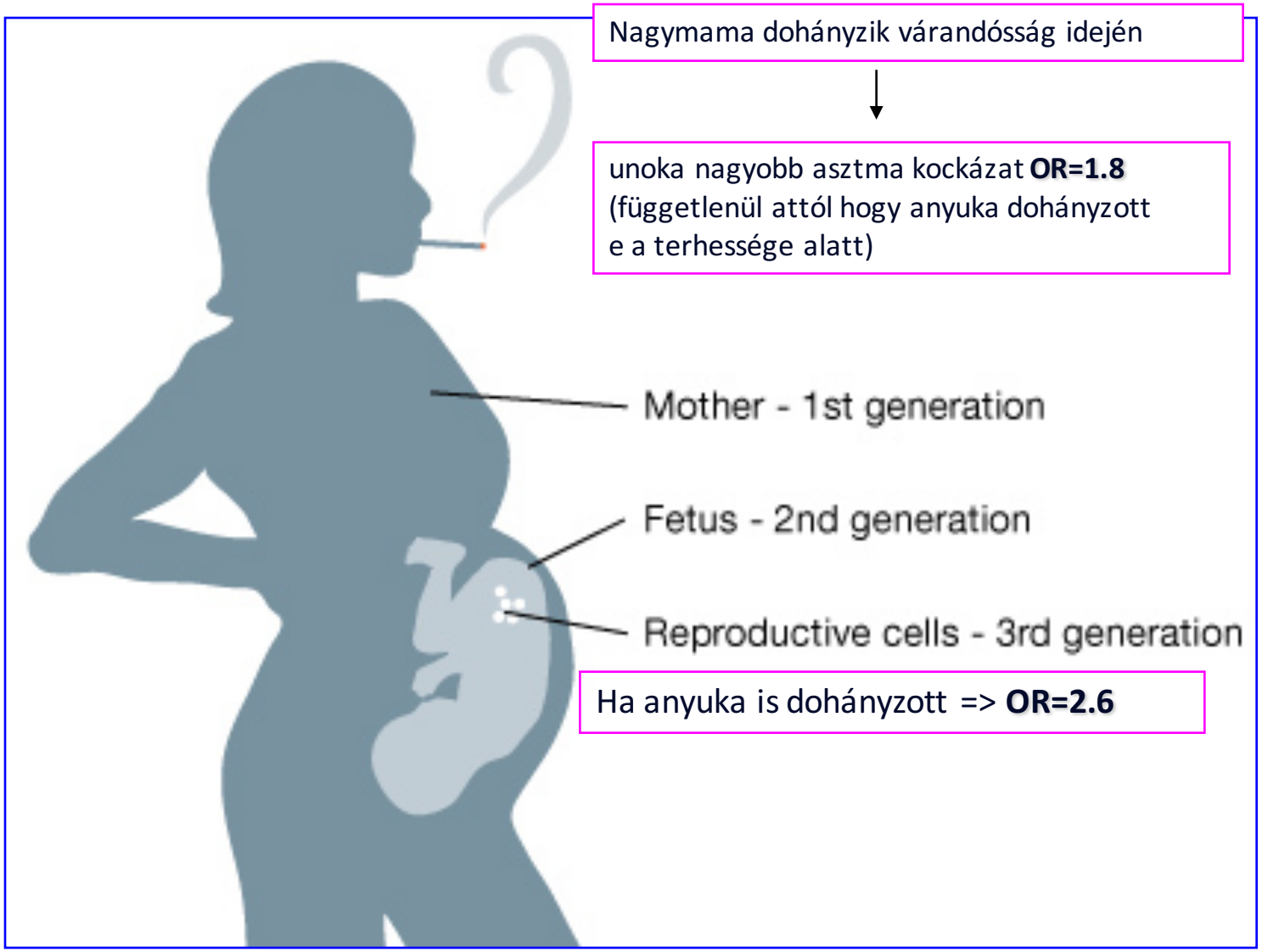
- ✓ ontogenesis-anyai hatás
- ✓ táplálkozás, hidratáció
- ✓ fizikai aktivitás
- ✓ gyógyszerek
- ✓ mérgek, dohányzás
- ✓ fertőzés, sugárzás
- ✓ fény
- ✓ zene
- ✓ stressz
- ✓ magatartási, lelki, meditatív hatások
- ✓ szociális környezet
- ✓ microbiota – együttélő mikróbák



Dr .Falus András ábrája alapján

Többgenerációs hatás

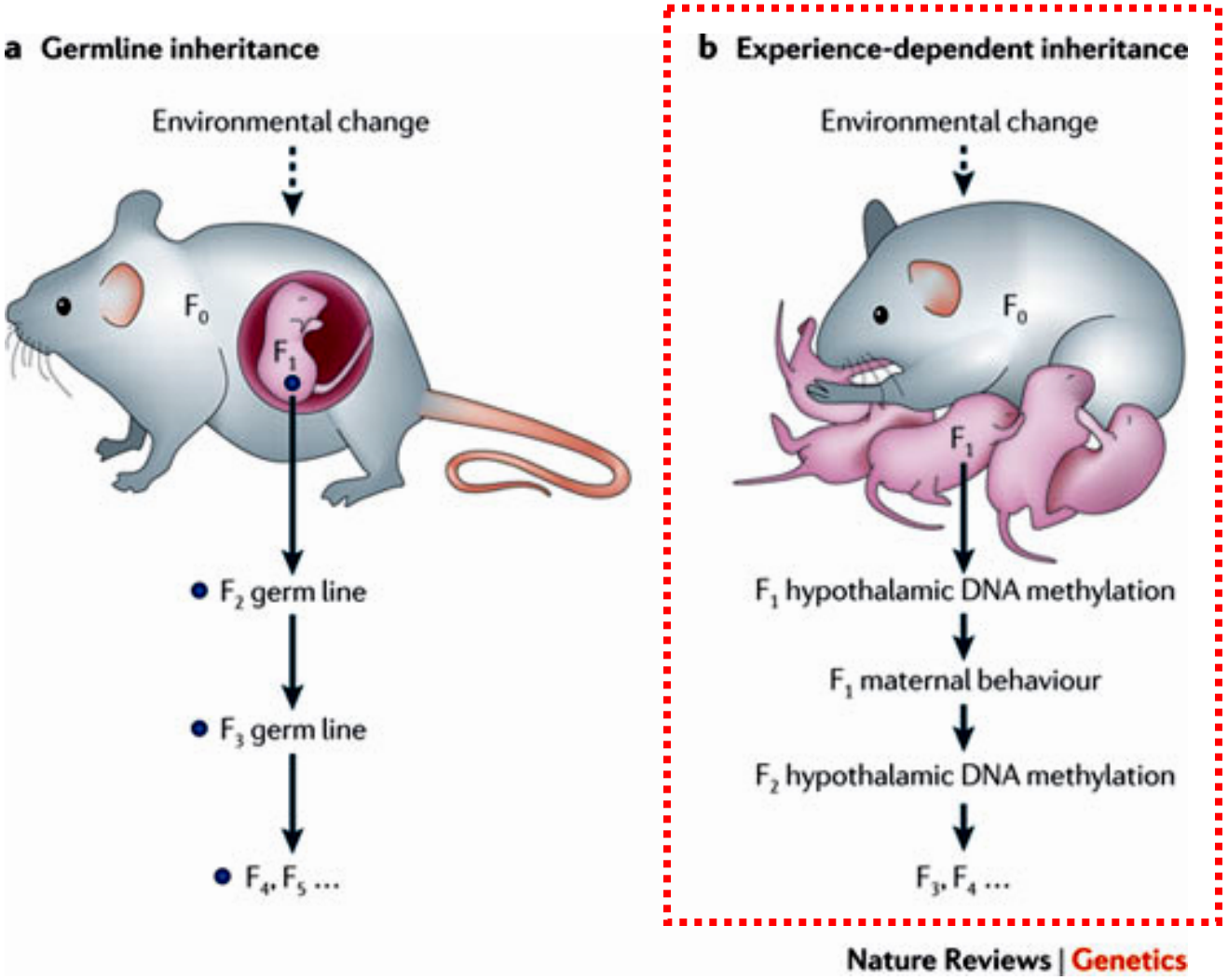
A dohányzás hatására kialakuló megnövekedett asztma-kockázat a második generációban is jelen van.



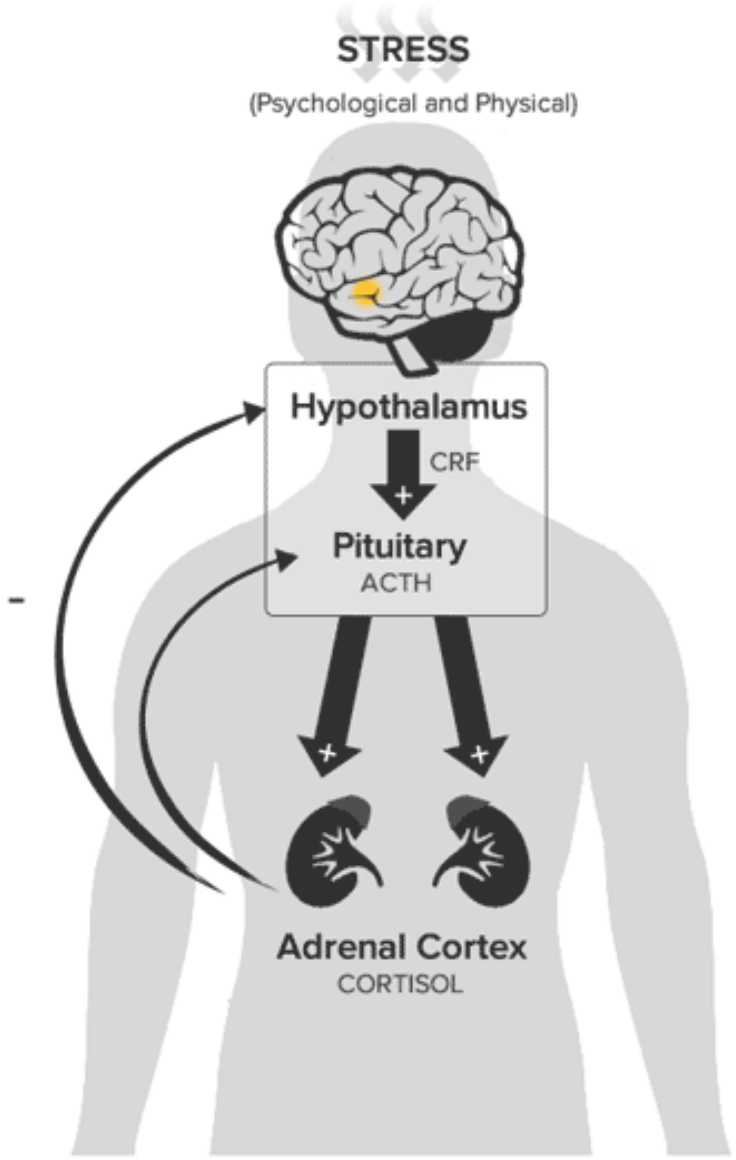
Li et al. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. Chest 2005;127:1232-1241

Dr .Falus András ábrája alapján

A transzgenerációs epigenetikai öröklődés alternatív lehetőségei



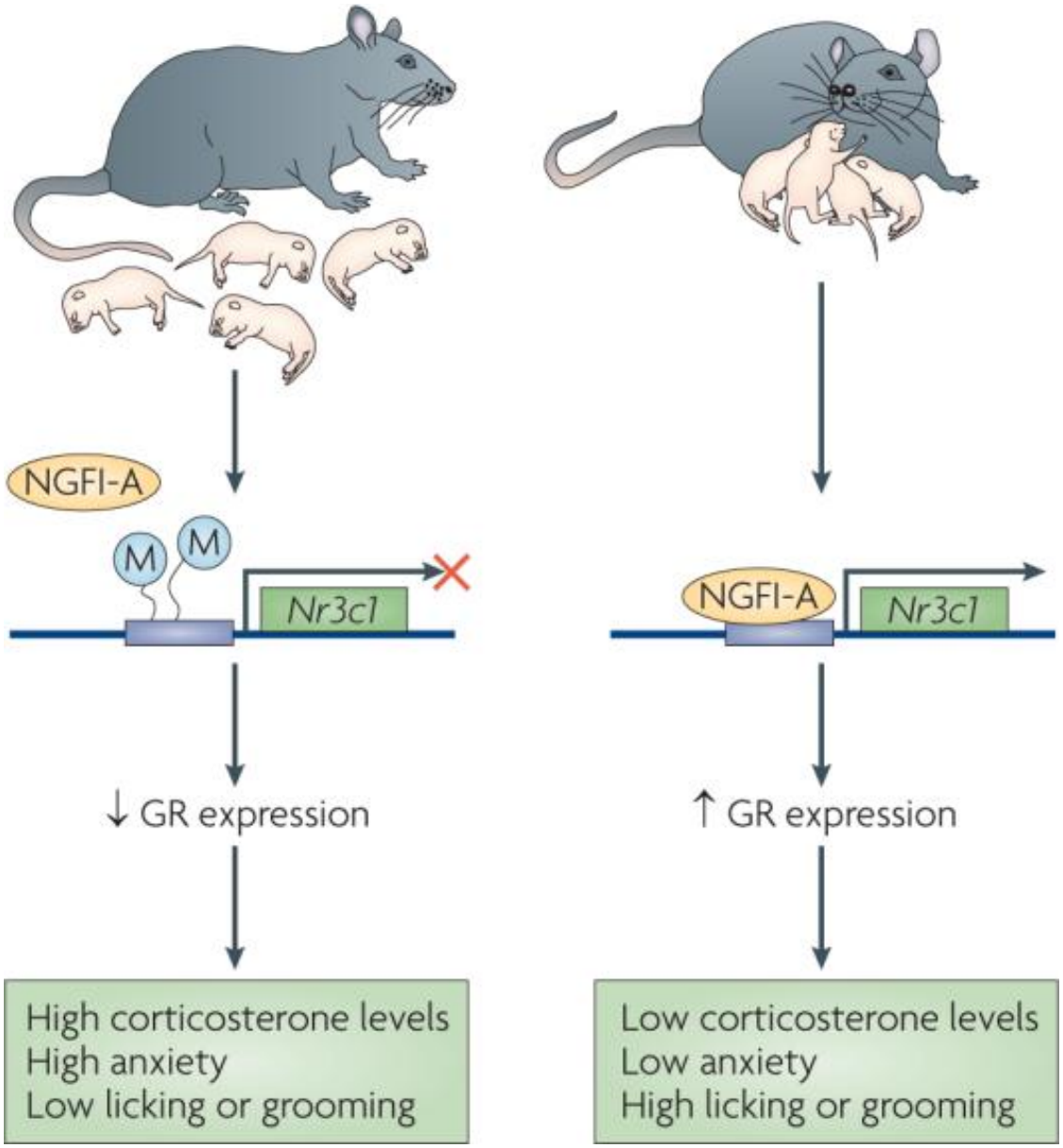
Pszichoszociális tényezők – stressz válasz

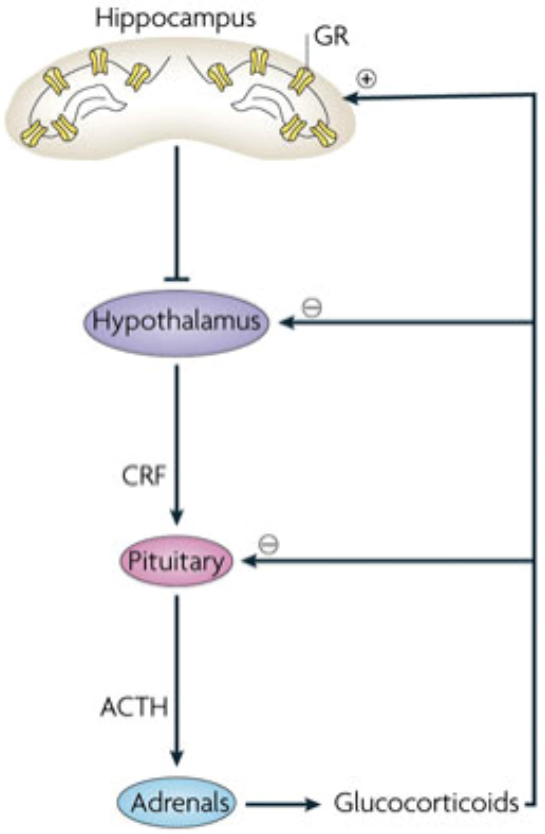


A hipotalamusz - hipofízis - mellékvesekéreg tengely

Anyai gondoskodás hatása

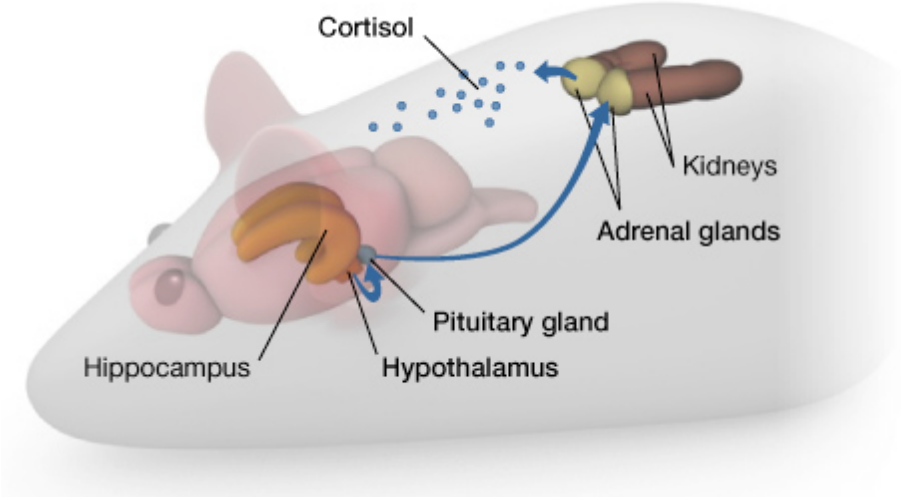
A stressz-érzékenység epigenetikai szabályozása



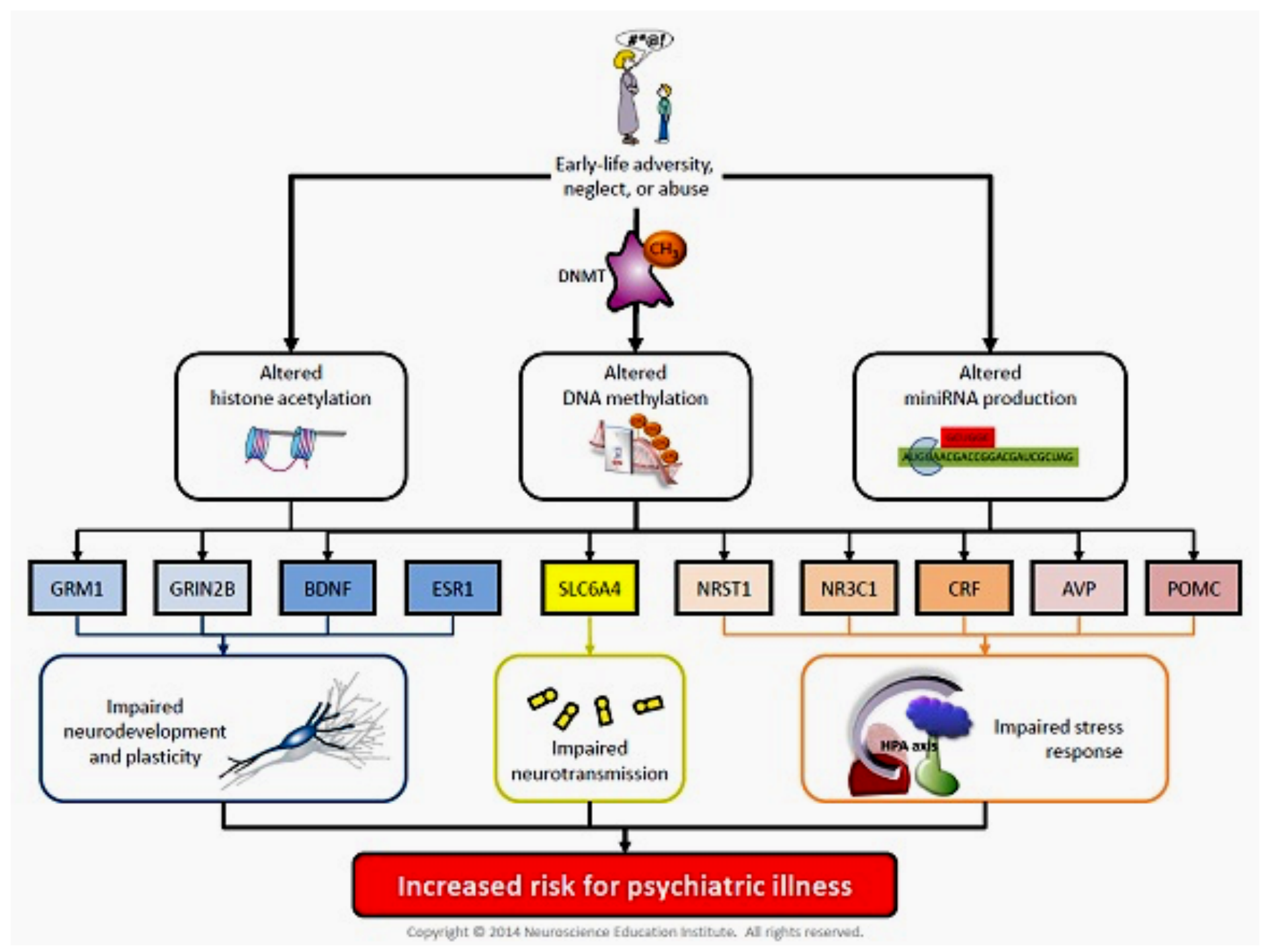


Nat Rev Neurosci. 2009 June; 10(6): 446–457.

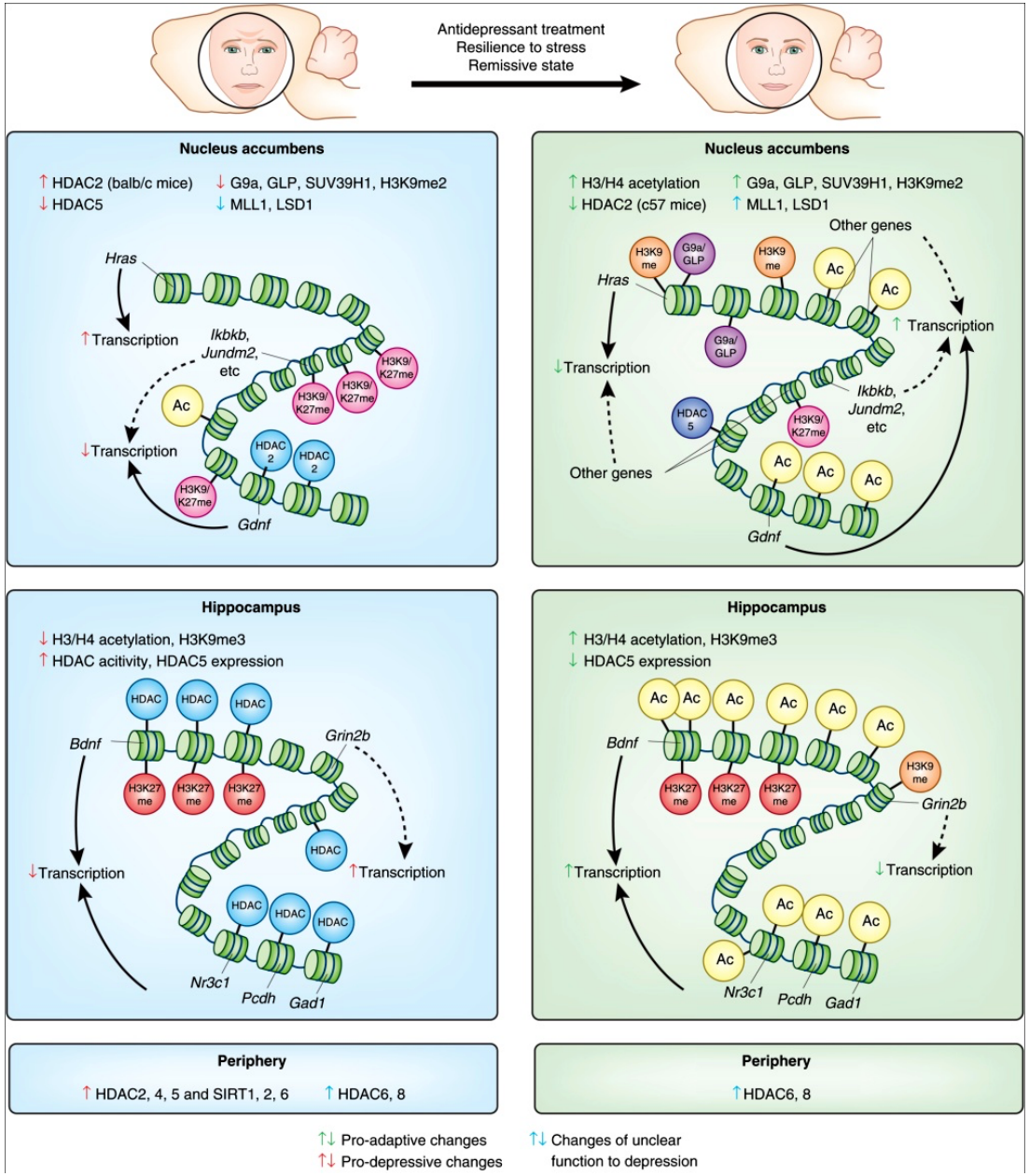
A glukokortikoid receptor segíti a stresszválasz lecsengését



http://learn.genetics.utah.edu/content/epigenetics/rats/



Epigenetikai módosulások depressziós agyban



Neuropsychopharmacology Reviews (2013) 38, 124-137;

Korai stressz és szociális védettség rágcsálókban

- Krónikus stressz az első trimeszterben
  - a GR exon 1_7 promoter metiláció ↑ a hypothalamuszban felnőtt hím utódokban[1]
- Szociális izolációban
  - kortizolszint ↑, immunológiai fittness ↓[2]
- Fizikailag gazdag és inspiráló környezetben
  - szinaptikus plaszticitást ↑, szorongásosság ↓, problémamegoldás ↑[3]
- Védett és pozitív ingerekben gazdag környezetben
  - cortizolszint és stressz gátolt szociális viselkedés javul[4]
  - javul az anyai viselkedés színvonala is[5,6]
- Gyermekkori gazdag, inspiratív környezet és felnőttkori egészség
  - BDNF csökkenés szintje csökken, idősköri tünetek kialakulása csökken[7]

[1]Mueller & Bale, T. L. (2008) J Neurosci 28(36), 9055–9065

[2]Gordon és mtsai (1992) Physiology and Behav 51(3), 467–472.

[3]Nithianantharajah & Hannan (2006). Nat Rev Neurosci 7(9),697–709)

[4]Morley-Fletcher és mtsai (2003) Eu J Neurosci18(12), 3367–3374).

[5,6]Bredy és mtsai (2003, 2004) Neurosci, 118(2), 571–576 Eu J Neurosci 20(5), 1355–1362

[7]Hockly és mtsai (2002) Ann Neurol 51(2), 235–242

Dr .Purebl György ábrája alapján

Depresszió - humán vizsgálatok

- Anyák magasabb depresszió pontszámmal a 3. trimeszterben
  - GR1F promoter metilációs szint ↑ a köldökzsinórvérben,
  - az első 3 élethónapban kortizol szint ↑[2]
- Gyermekkori abúzuson átesett öngyilkosok post mortem:
  - hippocampalis GR expresszió, ↓ GR1F promoter metiláció ↑[2]
- Depressziós állapotban elhunytak agyában:
  - hiszton acetiláció ↓ - csakúgy, mint szociálisan alulmaradt egerekében[3]

[1]Oberlander és mtsai (2008). Epigenetics, 3(2), 97–106

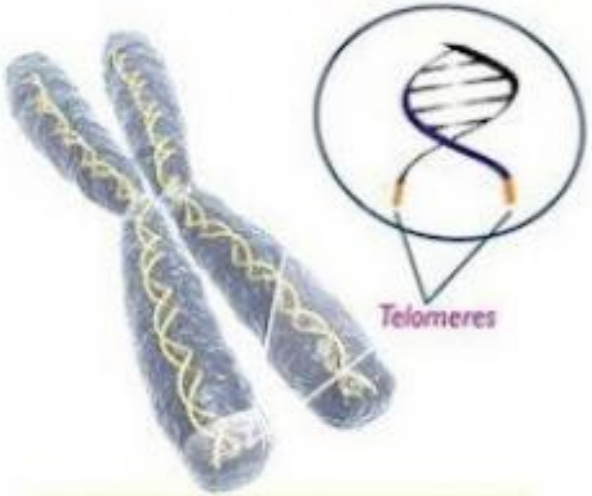
[2]McGowan és mtsai (2009). Nat Neurosci, 12(3), 342–348

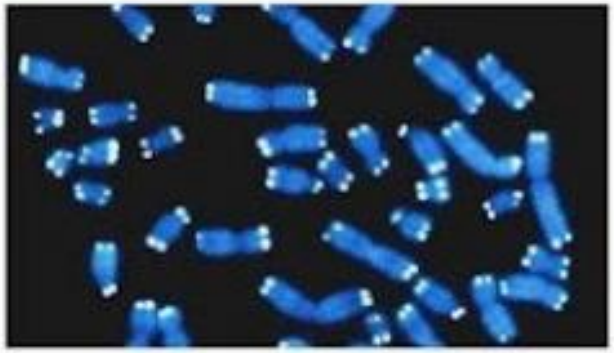
[3]Covington és mtsai (2009) J Neurosci 29(37), 11451–11460

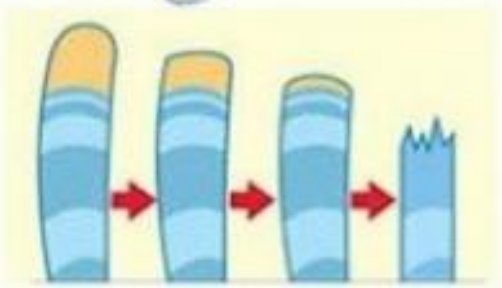
Dr .Purebl György ábrája alapján

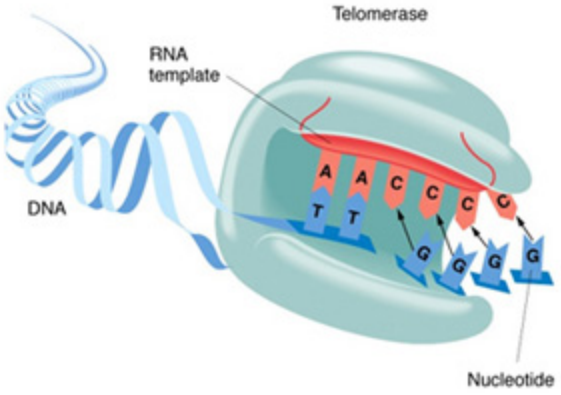
Telomérák és telomeráz

The Nobel Prize in Physiology or Medicine 2009

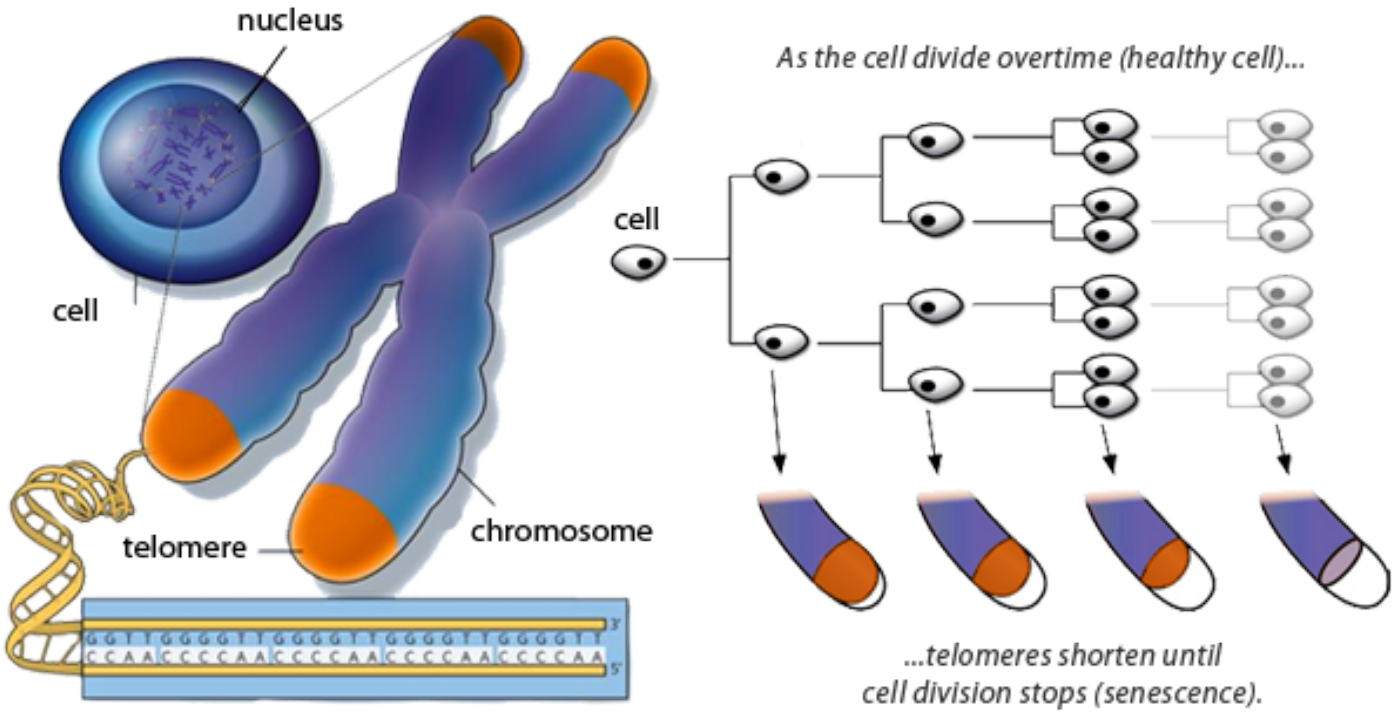




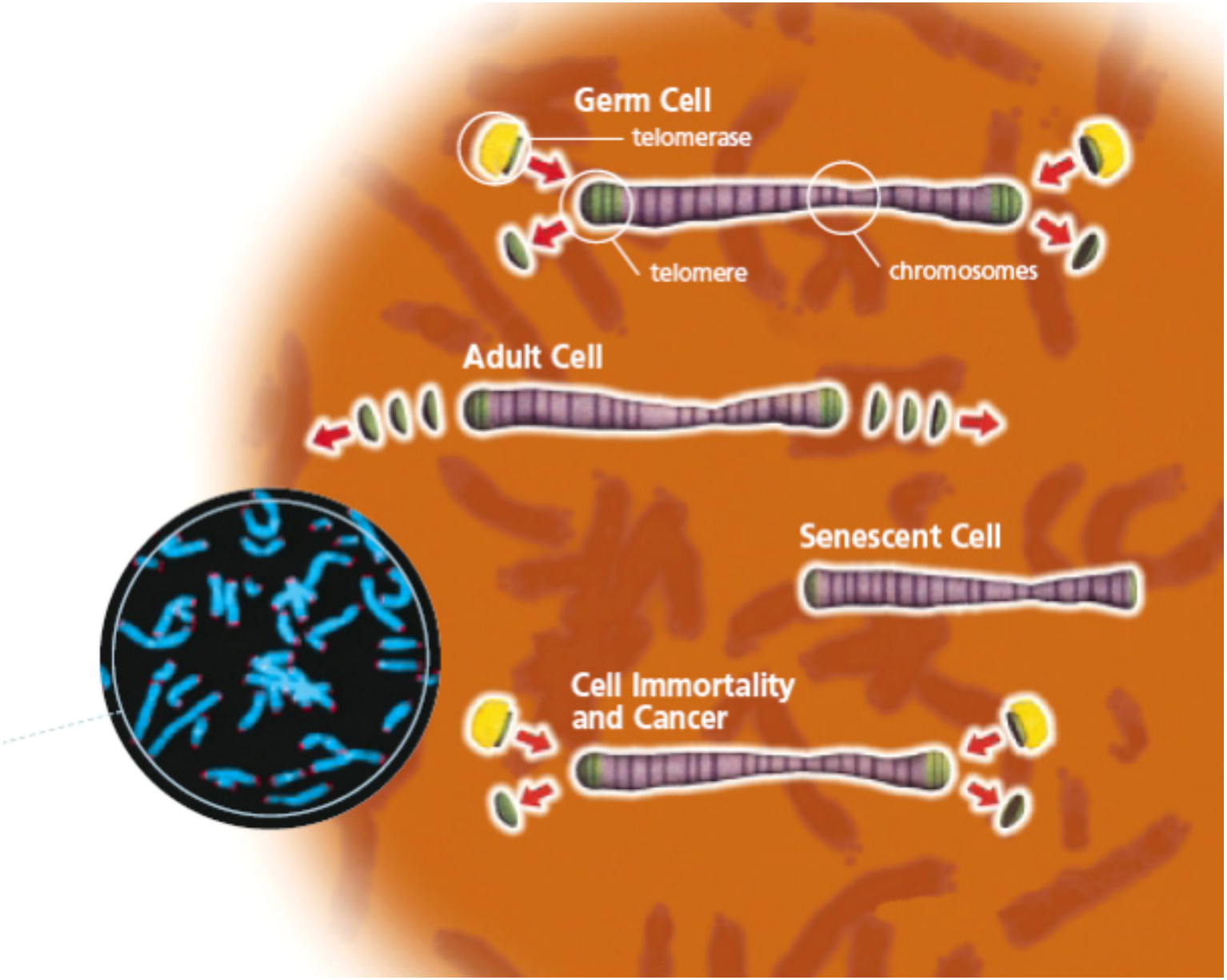




Egészséges testi sejtekben a telomérák osztódásról osztódásra rövidülnek



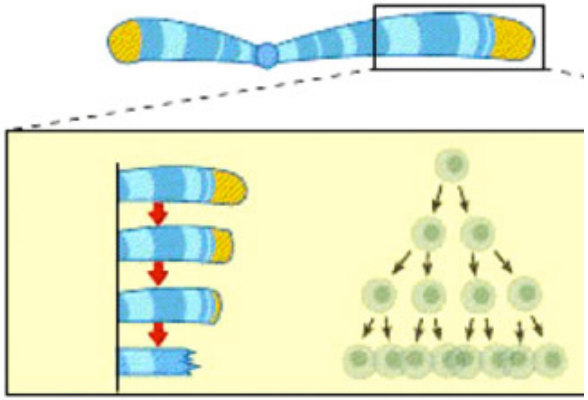
De vannak kivételek…



Telomér hossz és életmód összefüggések
Felgyorsult sejtszintű öregedés

- **Dohányzás** (Weischer et al. 2014)
- **Elhízás, inzulin rezisztencia** (Kim et. al, 2009)
- **Testmozgás** (Cherkas et al. 2006, Mirabello et. al. 2009., Chilton 2014)
- **Omega 3 a vérben** (Cassidy et al. 2010)
- **Vitaminok fogyasztása** (Mirabello et. al, 2009)
- **Alvásmennyiség** (Liang et al. 2011, Jackowska et al. 2012)

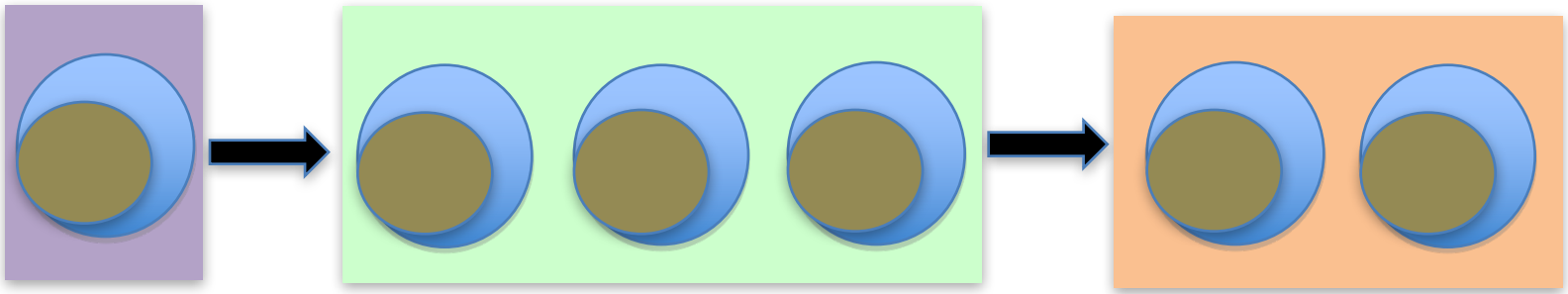
- **Észlelt stressz** (Epel et. al. 2004, Parks et. al. 2009)
- **Terhesség alatti stressz** (Entringer, 2011)
- **Szocioökonómiai státusz, SES** (Steptoe et. al. 2011)
- **Major depresszió** (Simon 2006, Wolkowitz 2011)
- **PTSD** (O'Donovan, 2011)



- **Alacsony telomeráz szint összefügg a főbb CVD rizikófaktorokkal** (Epel et al. 2008)

A

SOURCE	Bone marrow	thymus			Peripheral immune system	
CELL	lymphoid precursor	thymocytes			resting	activated

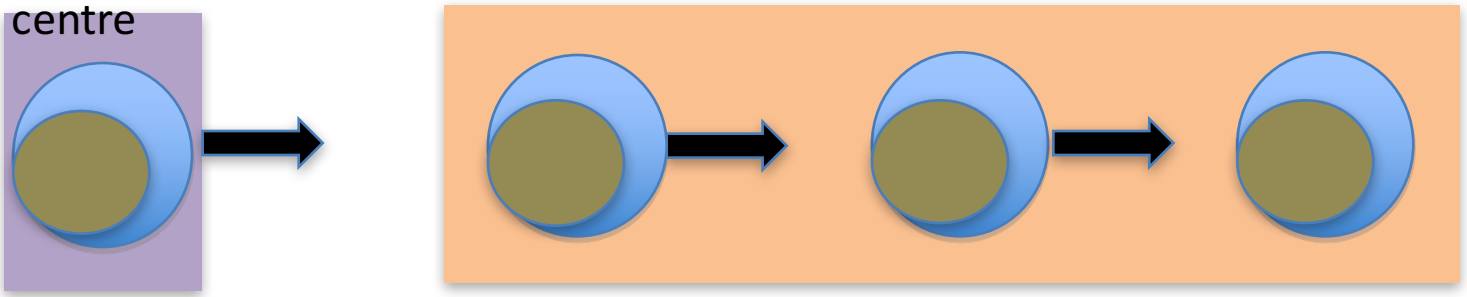


CD	34+	4-8-	4+8	4+8- 4-8+	4+8- 4-8+	4+8- 4-8+
TELOMERASE ACTIVITY						
	++++	**++++**	**++++**	**+++**	**(+)**	**++++**

B

SOURCE Bone marrow Peripheral immune system

CELL lymphoid precursor | naïve | Germinal-centre | memory cell



TELOMERASE ACTIVITY

++++ (+) ++++ +

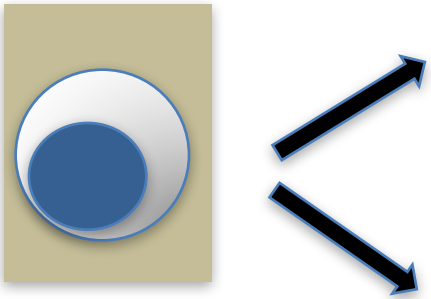
C

SOURCE Bone marrow Peripheral immune system

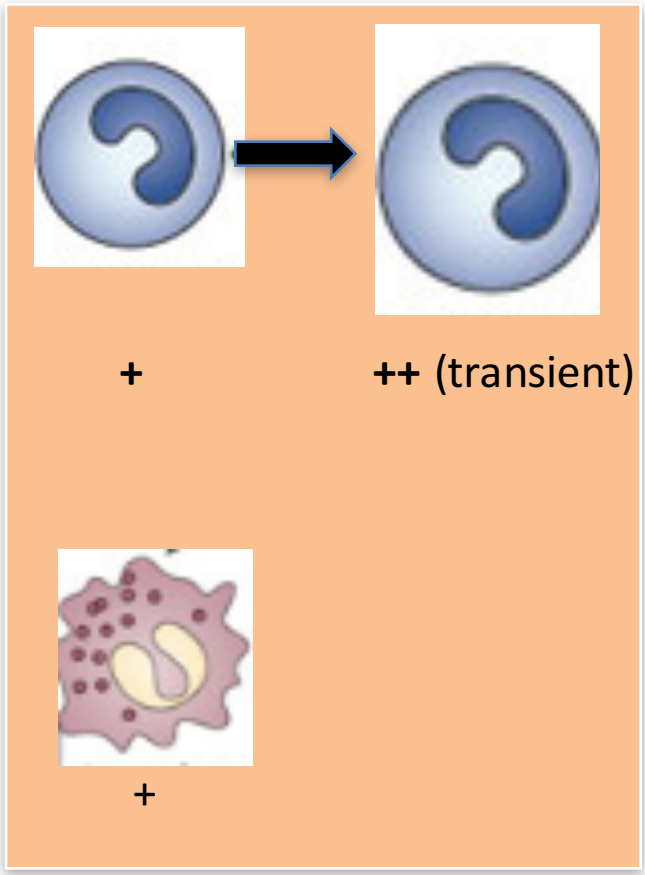
CELL myeloid precursor resting activated monocyte

monocyte

TELOMERASE ACTIVITY



++++



\+ ++ (transient)

\+

neutrophil granulocyte

Krónikus stressz

Psychosocial Factors: Chronic Psychological Stress

Author	Date	Samples	Method	Findings
Epel et al.	2004	39 mothers with chronically ill children 19 mothers with healthy children	qPCR	Chronicity and perceived stress associated with telomere attrition (Equivalent to up to 17 years accelerated aging)
Damjanovich et al.	2007	41 caregivers of patients with AD 41 controls, age and gender matched	Southern blot	Telomere attrition in caregivers (loss of 6.2–6.4 kb compared with controls)
O'Donovan et al.	2009	36 female healthy postmenopausal caregivers and noncaregivers	qPCR	Pessimism independently associated with shorter LTL
Parks et al.	2009	647 women Sisters of women with breast cancer	qPCR	Perceived stress modestly associated with telomere attrition and stress hormones
Humphreys et al.	2011	61 women exposed to interpartner violence 41 healthy female controls	qPCR	Telomere attrition in those exposed to interpartner violence Length of time in the abusive relationship and having children associated with shortened telomeres

Puterman E, Epel E. , Soc Personal Psychol Compass, 2012 An intricate dance: Life experience, multisystem resiliency, and rate of telomere decline throughout the lifespan.

Gyermekkori bántalmazás

Psychosocial Factors: Childhood Maltreatment

Authors	Date	Samples	Method	Findings
Tyrka et al.	2010	31 adults with no current or past major Axis I psychiatric disorders (10 reported moderate to severe maltreatment and 21 reported no maltreatment)	qPCR	Telomere attrition in those exposed to childhood neglect (not abuse)
Glass et al.	2010	Reported childhood maltreatment (123 cases vs. 1751 controls) Reported childhood maltreatment and sexual abuse (34 cases vs. 516 controls) Reported childhood maltreatment and physical abuse (20 cases vs. 520 controls)	Southern blot	Childhood maltreatment not linked to telomere attrition
Kananen et al.	2010	321 anxiety disorder 653 matched controls 30–87 years	qPCR	Shorter telomere length associated with a greater number of childhood adverse life events in both groups Significant age- and sex-adjusted effect of number of childhood adversities on LTL in adulthood
Surtees et al.	2011	4,441 women UK European Prospective Investigation into Cancer–Norfolk Study	qPCR	Adverse childhood experiences associated with shorter LTL Each additional childhood adversity equivalent to an approximate 3-year increase in aging
Kiecolt-Glaser et al.	2011	132 healthy older adults Community sample (58 were dementia family caregivers and 74 were noncaregivers)	qPCR	Multiple childhood adversities related to increased IL-6 Multiple childhood adversities related to shorter telomeres (telomere difference equivalent to 7–15 years shortened lifespan)
Shalev et al.	2013	236 children Environmental-Risk Longitudinal Twin Study	qPCR	Significantly more telomere erosion between the ages of 5 and 10 years in children who experienced two or more kinds of violence compared with participants exposed to one type or no violence

Fizikai aktivitás

Behavioral Factors: Physical Activity

Authors	Date	Sample	Method	Findings
Ludlow et al.	2008	34 men and 35 women 50–70 years	qPCR	Moderate levels of physical activity (but not strenuous levels) significantly associated with longer LTL
Cherkas et al.	2008	2,152 women and 249 men Healthy twin volunteers	qPCR	LTLs of the most active participants 200 nucleotides longer than those of the least active subjects
Puterman et al.	2010	63 healthy, postmenopausal women	qPCR	Among nonexercisers, a 1-unit increase in perceived stress related to a 15-fold increase in the odds of having short telomeres Among exercisers, perceived stress unrelated to TL
LaRocca et al.	2010	15 sedentary young (18–32 years) 15 sedentary older (55–72 years) 10 endurance exercise-trained young 17 endurance exercise-trained older	qPCR	LTL shorter in the older vs. young sedentary adults LTL of the older endurance-trained adults 900 base pairs greater than that of their sedentary peers and not significantly different from that of young exercise-trained adults
Savela et al.	2012	204 men Helsinki Businessmen Study	Southern blot	Longer LTL in men in the moderate physical activity group than in the low or high physical activity group
Denham et al.	2013	67 ultra-marathon runners 56 healthy male controls	qPCR	Significantly longer LTL in ultra-marathon runners compared with controls
Du et al.	2012	7,813 women Nurses' Health Study 43–70 years old	qPCR	Greater moderate to vigorous intensity activity associated with increased LTL (especially calisthenics/aerobics)
Mathur et al.	2013	17 marathon runners 15 sedentary controls Age- and sex-matched controls	qPCR	Similar lymphocyte and granulocyte TL in athletes and sedentary controls

Ludlow AT, Ludlow LW, Roth SM, Biomed Res Int (2013)
Do telomeres adapt to physiological stress? Exploring the effect of exercise on telomere length and telomere-related proteins.

Lifang Hou et al. (2015) **Blood Telomere Length Attrition and Cancer Development in the Normative Aging Study Cohort**, Ebiomedicine, doi:10.1016/j.ebiom.2015.04.008

Changes in chromosomes years before cancer diagnosis could yield biomarker to predict cancer

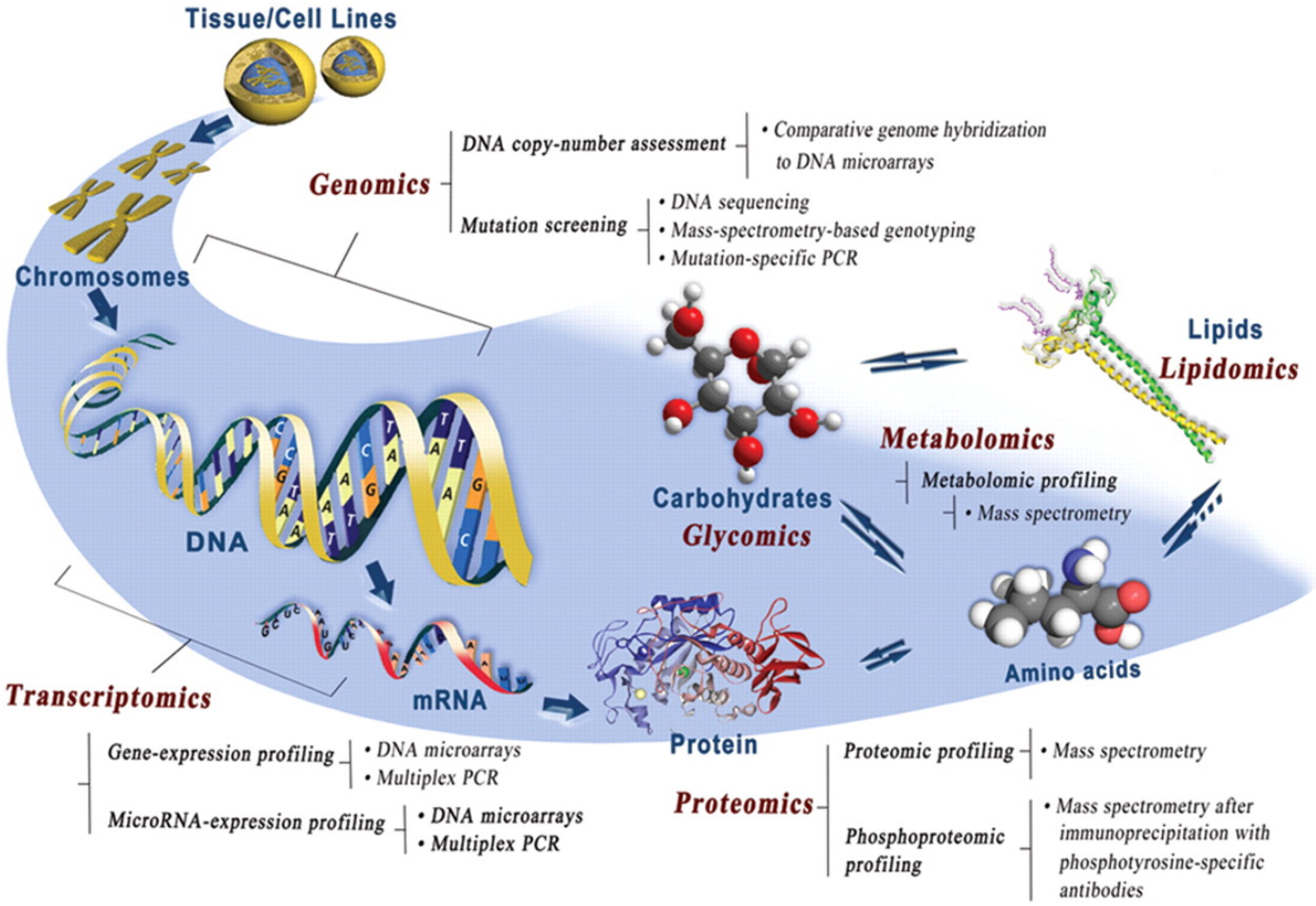
http://www.northwestern.edu/newscenter/stories/2015/04/telomere-changes-predict-cancer.html

Genetic changes can predict cancer up to 13 years in the future, according to new research

http://www.telegraph.co.uk/news/11574893/New-test-can-predict-cancer-up-to-13-years-before-disease-develops.html


www.twin2014.eu
Budapest
Hungary
NOVEMBER 2014
16th 19th
Twins
2014
The Joint 3rd World Congress on
Twin Pregnancy
a Global Perspective
&
The 15th Congress of the
International Society
Twin Studies (ISTS)

What twin studies tell us about (human) omics



The EpiTwin Project

www.epitwin.eu

DNA methylation whole blood profiles in 5,000 UK Twins using DNA methylation sequencing and microarrays.

Aim: To identify Differentially Methylated Regions (DMRs) in common complex disease

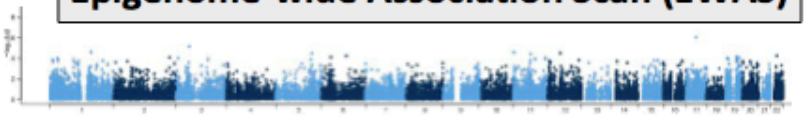
Methylation sequence data

⇩

10M methylation sites, 5000 individuals

⇩

Epigenome-wide Association Scan (EWAS)

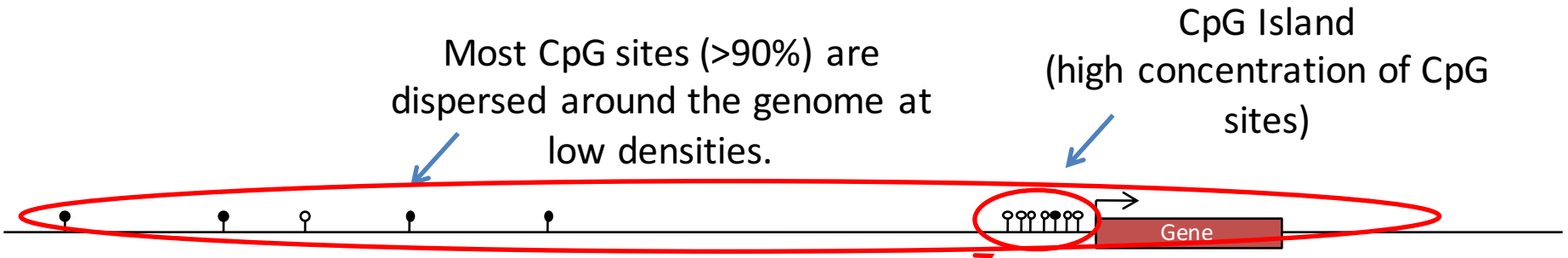


⇩

Differentially Methylated Regions (DMRs) in Disease

Pain sensitivity
Lipids
Autoimmune disease
Type 2 Diabetes
Osteoporosis
Alcohol use
Allergy
Heart Disease
Depression
Muscle mass
Psoriasis
Eczema
Colon cancer
Osteoarthritis
Bone mineral density
Breast Cancer
Hypertension
Asthma
Obesity
IVF
Telomeres

DNA methylation platforms - discovery

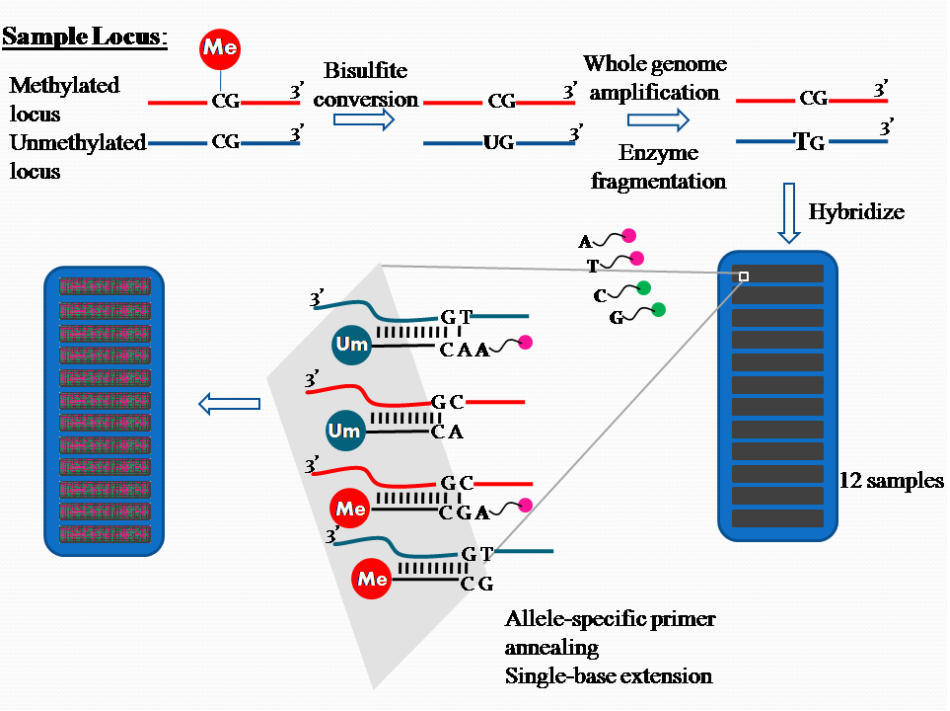


The Infinium HumanMethylation450 array targets all regions

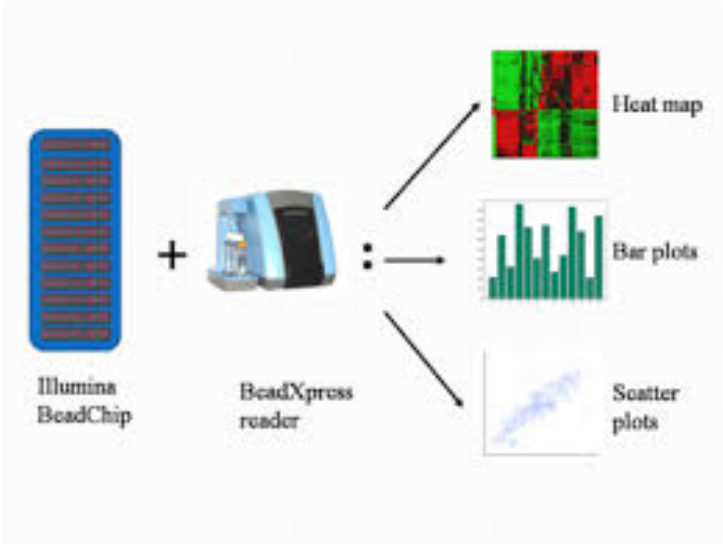
The Infinium HumanMethylation27 array targets promoter regions

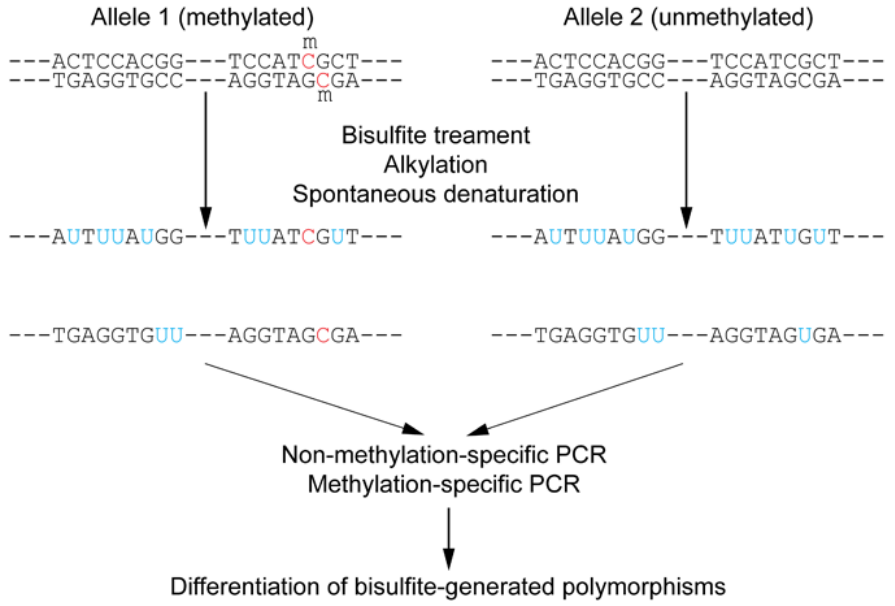
Genome-wide DNA methylation analysis

- Infinium Human Methylation27 (HM27) and HM450 bead arrays
- 27,000 CpG sites, 14,500 genes or 486000 CpG sites – all genes
- 12 samples / array (~$500 / sample)



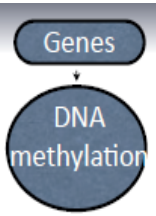
Illumina 450k





Bisulphite sequencing

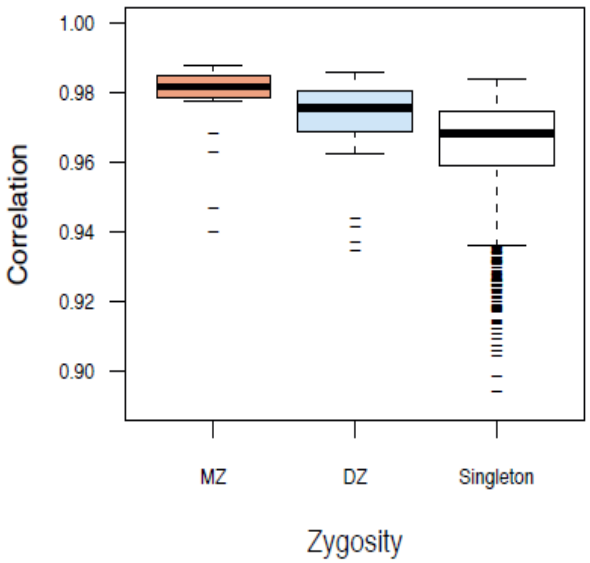
DNA methylation heritability



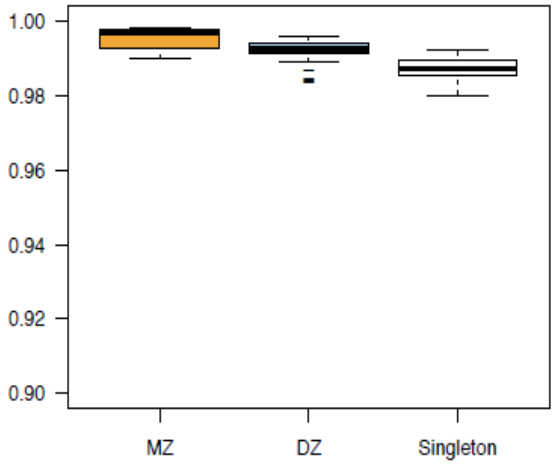
- Whole blood samples from 172 female twins
- 24,000 methylation sites
- Aim to assess DNA methylation heritability

- Whole blood samples from 100 female twins
- 468,000 methylation sites
- Aim to assess DNA methylation heritability

Illumina 27k



Illumina 450k



➡ The mean estimate of CpG-site heritability is 0.18. Consistent findings on Illumina 450k.

[1] Bell et al. 2012 PLoS Genetics

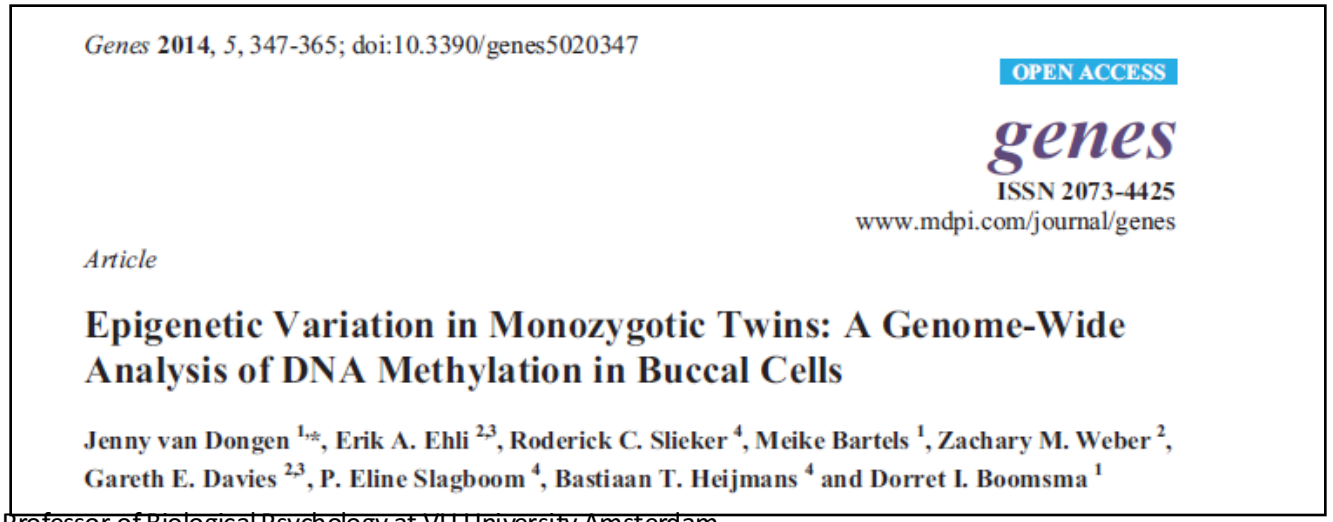
Twin studies of DNA methylation

Heritability of DNA methylation (average of genome-wide CpGs):

- 18 % in blood (*Bell J.T. et al 2012 PLoS. Genet.*)
- 5% in placenta, 7% in human umbilical vascular endothelial cells (HUVEC), 12% in cord-blood mononuclear cells (CBMC) from neonatal twins (*Gordon L. et al 2012 Genome Res)*
- 19% in adipose tissue in adult female twins (*Grundberg E. et al 2013 AJHGenet.)*
- 20% (also transgenerational) in whole blood (*McRae AF et al. 2014 Genome Biol*.)

Study of buccal cell DNA:

- MZ twin correlations for genome-wide methylation in buccal cells
- Variation between genomic regions? (e.g. CpG islands, promoters, gene bodies etc)



Genes **2014**, *5*, 347-365; doi:10.3390/genes5020347

OPEN ACCESS

genes

ISSN 2073-4425

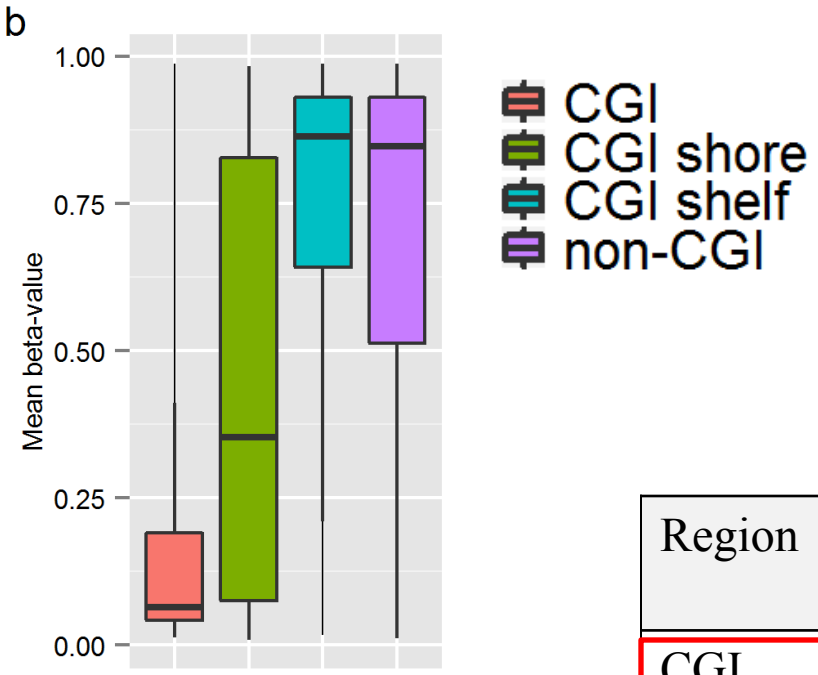
www.mdpi.com/journal/genes

Article

Epigenetic Variation in Monozygotic Twins: A Genome-Wide Analysis of DNA Methylation in Buccal Cells

Jenny van Dongen [1,*], Erik A. Ehli [2,3], Roderick C. Slieker [4], Meike Bartels [1], Zachary M. Weber [2], Gareth E. Davies [2,3], P. Eline Slagboom [4], Bastiaan T. Heijmans [4] and Dorret I. Boomsma [1]

Dorret Boomsma m Professor of Biological Psychology at VU University Amsterdam

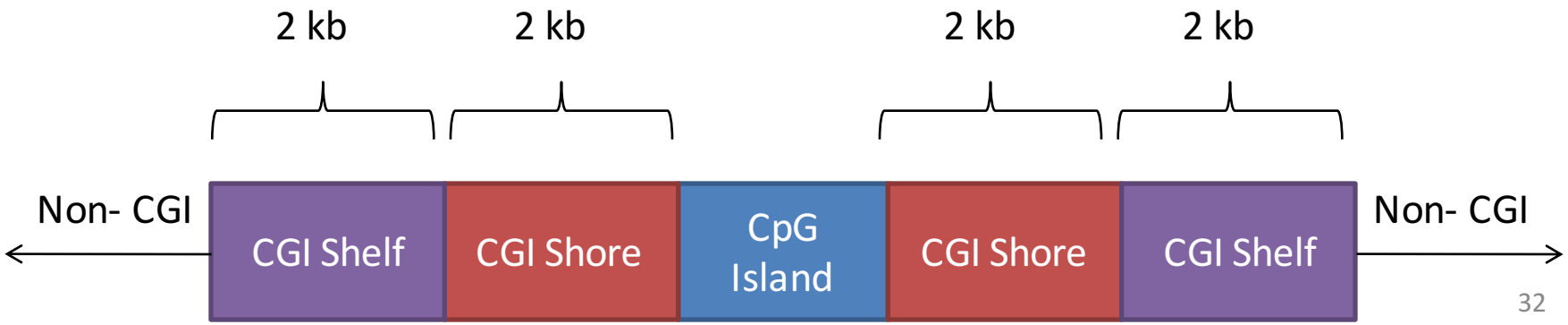


CGI= CpG Island

420,921 CpGs

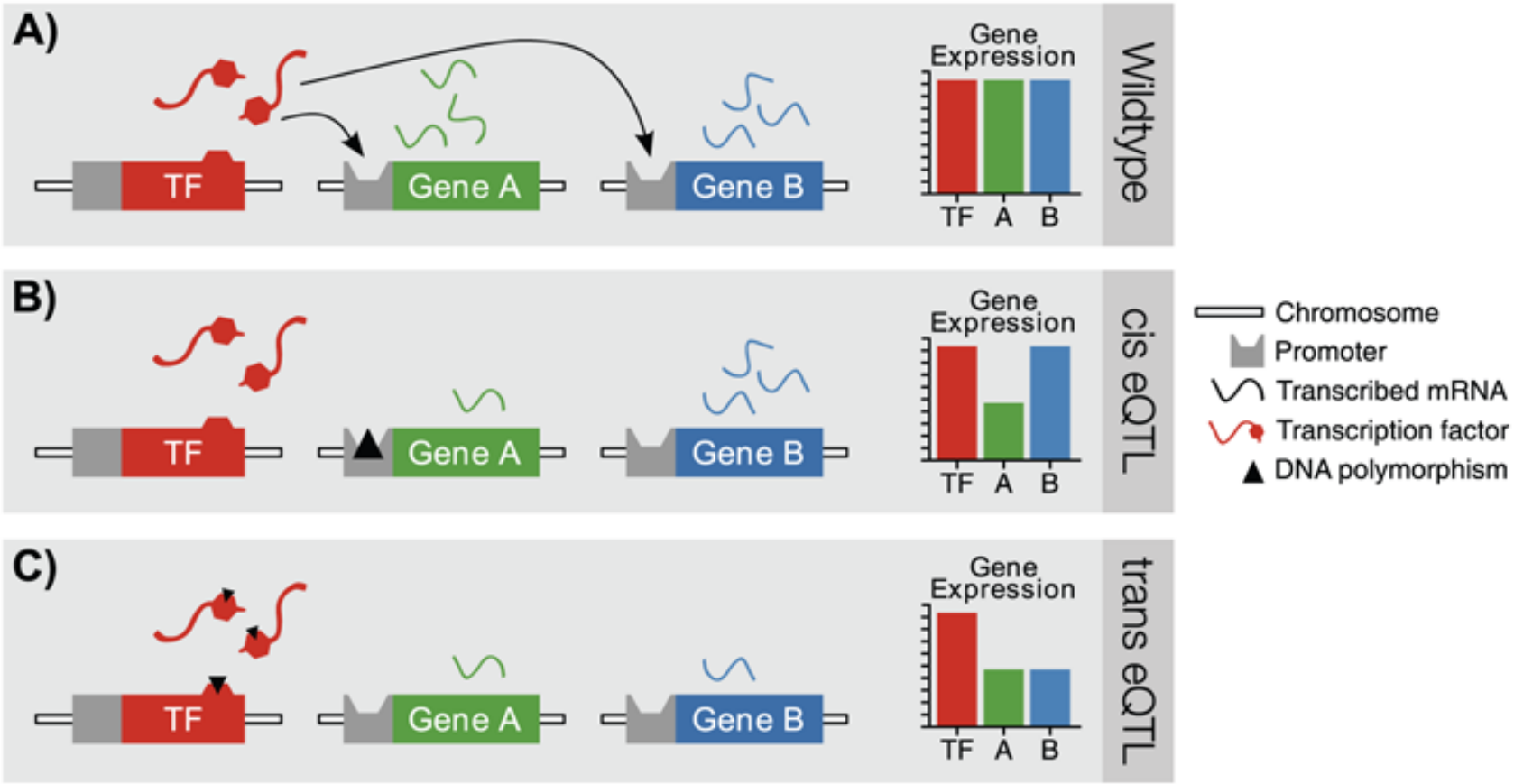
Illumina 450k

Region	% of CpGs	Mean **MZ cor**	Median **MZ cor**
CGI	17.9%	0.66	0.73
CGI shore	25.1%	0.54	0.55
CGI shelf	10.2%	0.50	0.49
Non-CGI	46.9%	0.49	0.47



*Dorret Boomsma*m Professor of Biological Psychology at VU University Amsterdam

eQTL: Expression quantitative trait loci are genomic loci that regulate expression levels of mRNAs



Alcohol Research: *Current Reviews*, Volume 34, Issue Number 3

ARTICLES

nature genetics

Heritability and genomics of gene expression in peripheral blood

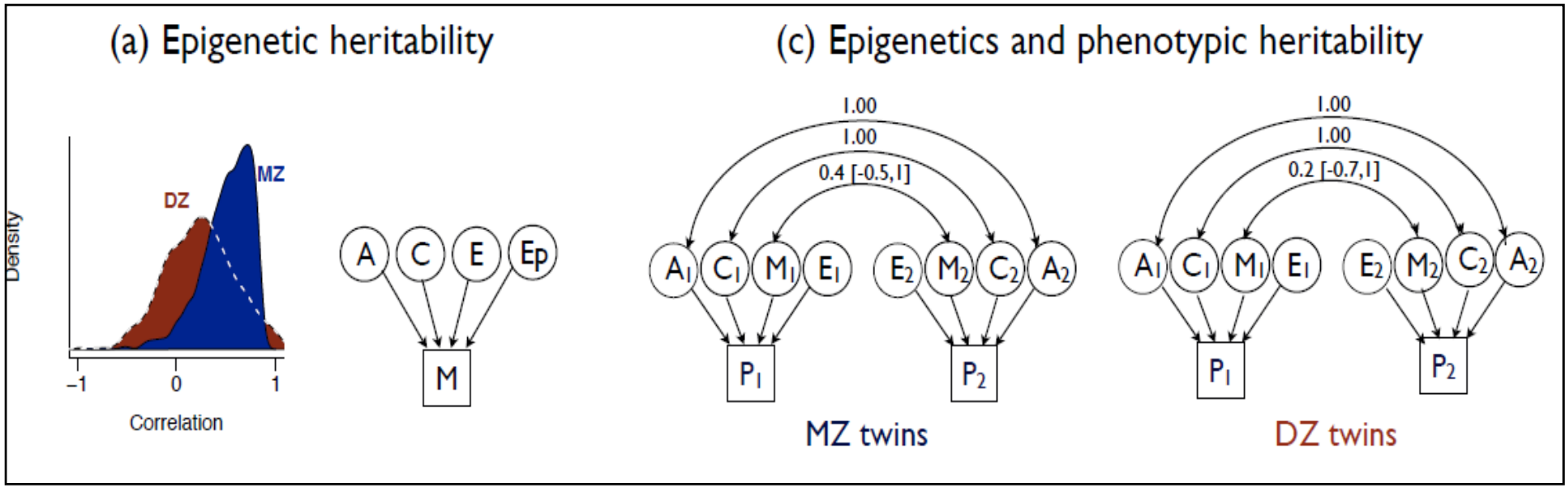
Fred A Wright[1–3,13], Patrick F Sullivan[4,13], Andrew I Brooks[5], Fei Zou[6], Wei Sun[6], Kai Xia[6], Vered Madar[6], Rick Jansen[7], Wonil Chung[6], Yi-Hui Zhou[1,2], Abdel Abdellaoui[8], Sandra Batista[9], Casey Butler[9], Guanhua Chen[6], Ting-Huei Chen[6], David D'Ambrosio[10], Paul Gallins[4], Min Jin Ha[6], Jouke Jan Hottenga[8], Shunping Huang[9], Mathijs Kattenberg[8], Jaspreet Kochar[10], Christel M Middeldorp[8], Ani Qu[10], Andrey Shabalin[11], Jay Tischfield[5], Laura Todd[4], Jung-Ying Tzeng[1,2], Gerard van Grootheest[7], Jacqueline M Vink[8], Qi Wang[10], Wei Wang[12], Weibo Wang[9], Gonneke Willemsen[8], Johannes H Smit[7], Eco J de Geus[8], Zhaoyu Yin[6], Brenda W J H Penninx[7] & Dorret I Boomsma[8]

VOLUME 46 | NUMBER 5 | MAY 2014 NATURE GENETICS

We conducted a combined study of twin heritability of expression and eQTLs
(N = 2752 twins (NTR) + N = 1895 (NESDA)

*Dorret Boomsma*m Professor of Biological Psychology at VU University Amsterdam

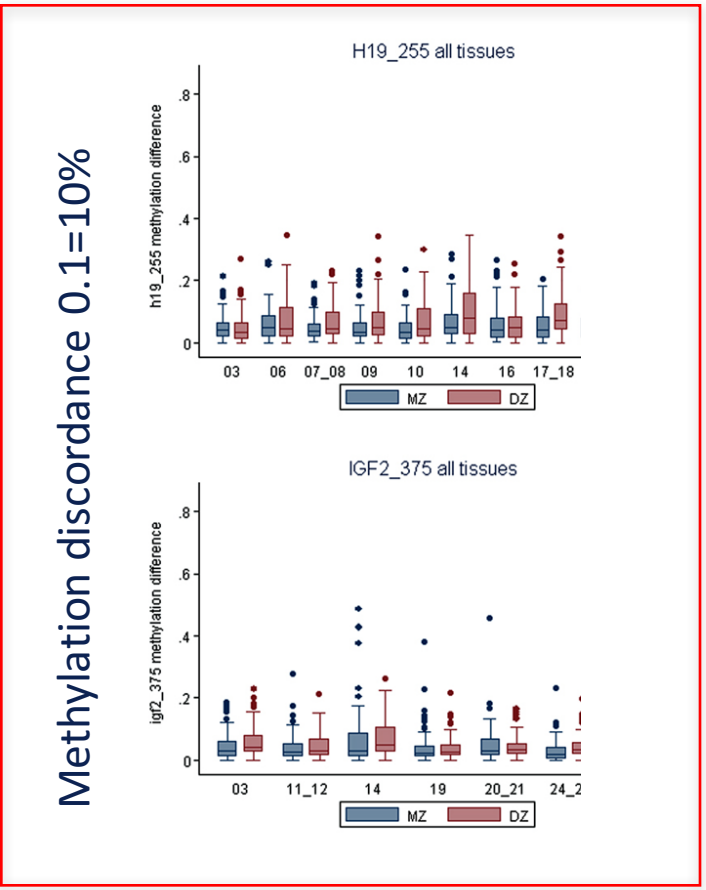
Epigenetic heritability and Twins

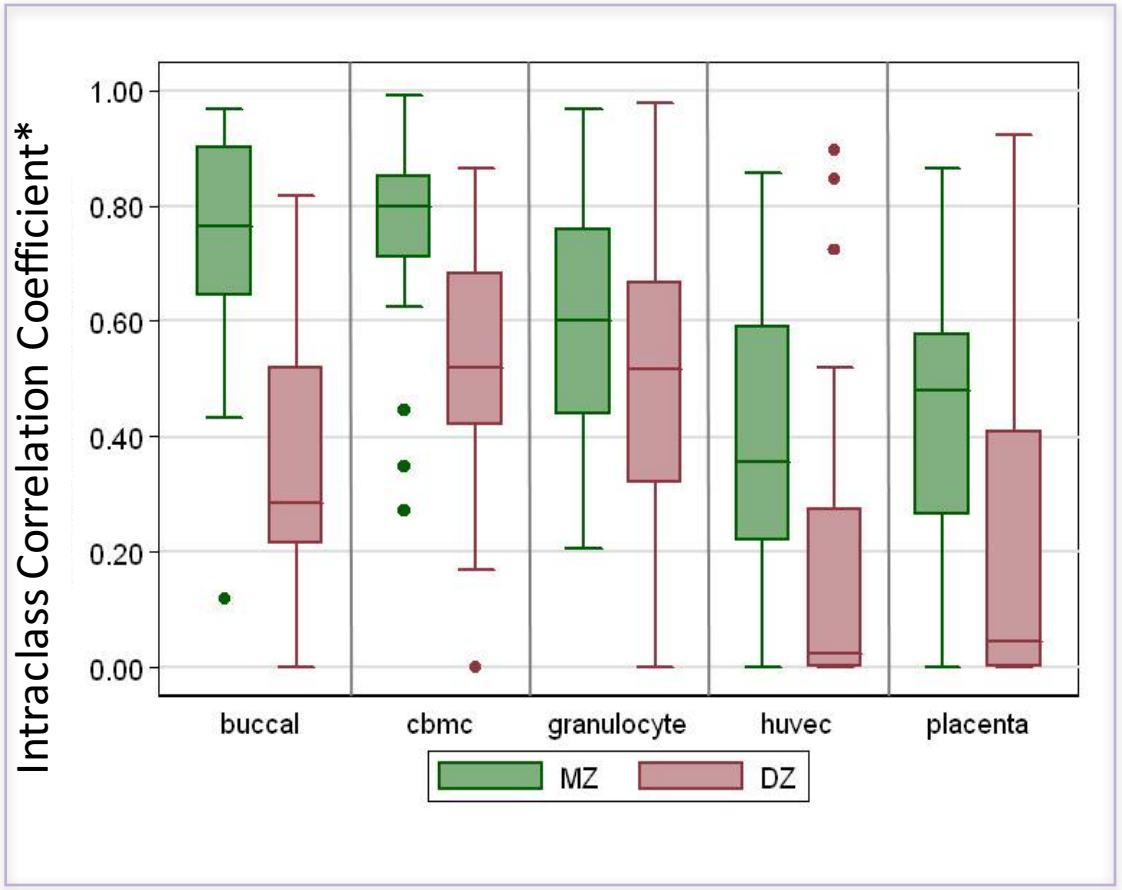


H2 = ~20% overall but probably greater for key regulatory areas

Bell & Spector TIG 2011

Locus specific methylation analysis in newborn twins





- MZ twins show considerable methylation variation within pairs
- DZ twins are generally less similar in methylation profile c/f MZ pairs

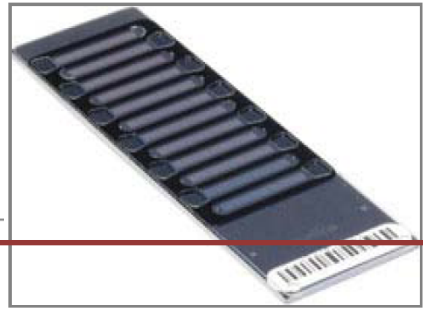
Human Molecular Genetics, 2010, Vol. 19, No. 21 **4176–4188**
doi:10.1093/hmg/ddq336
Advance Access published on August 10, 2010

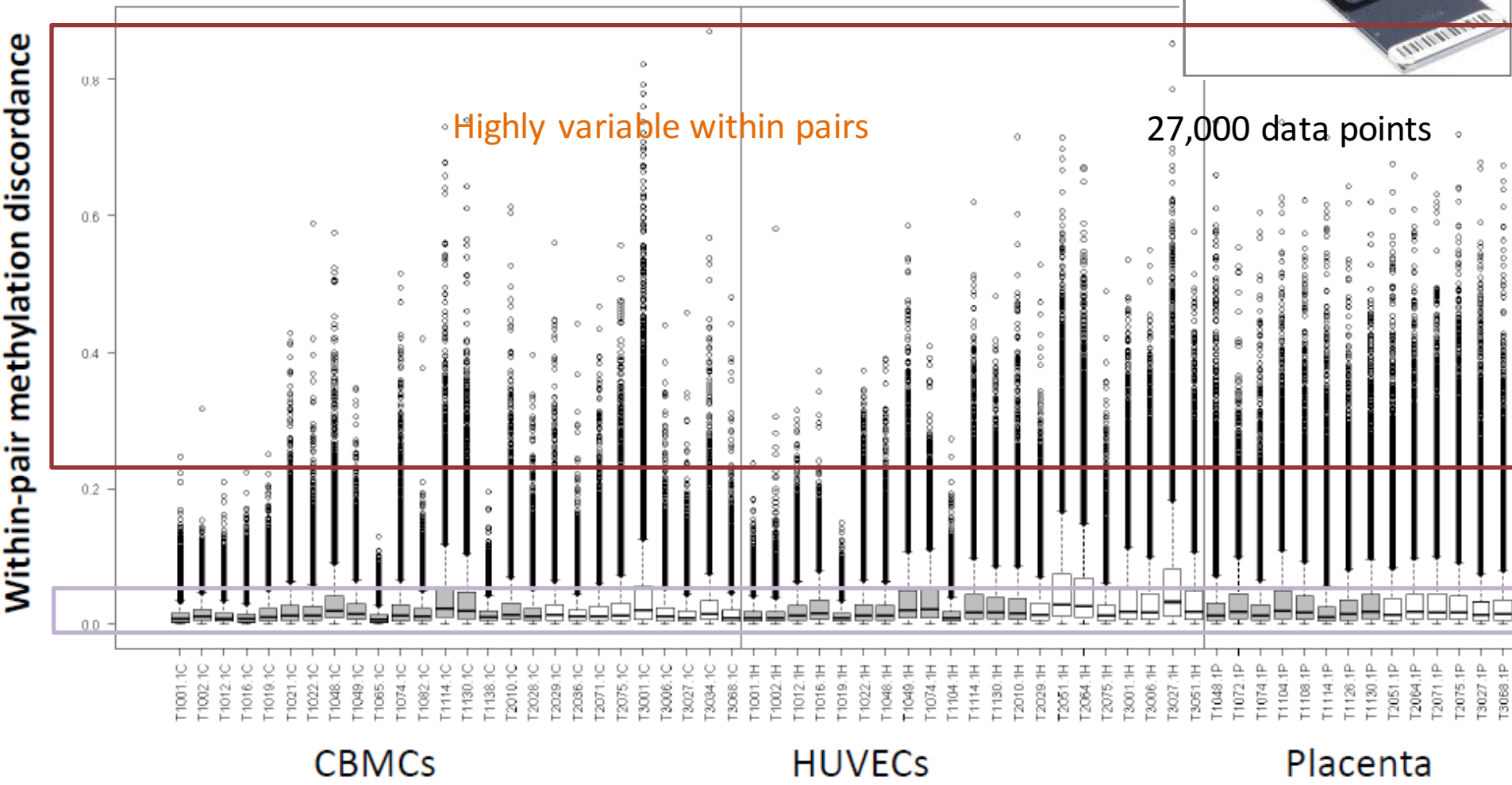
DNA methylation analysis of multiple tissues from newborn twins reveals both genetic and intrauterine components to variation in the human neonatal epigenome

Miina Ollikainen[1,3], Katherine R. Smith[2], Eric Ji-Hoon Joo[1,3], Hong Kiat Ng[1,3], Roberta Andronikos[1,3], Boris Novakovic[1,3], Nur Khairunnisa Abdul Aziz[1,3], John B. Carlin[2,3],

Genome-wide methylation data

- evidence of environmental effects





Clear evidence of variability within MZ twins

Summary

- Variation in DNA methylation in MZ twins at birth highlights the importance of non-shared *in utero* environment in specifying neonatal epigenetic profile

- The generally greater epigenetic discordance in DZ twins highlights the role of genetic variation in regulating neonatal epigenome in humans

- Sites and magnitude of difference vary according to tissue and gestational age

- Other similar data are emerging

Neonatal DNA methylation profile in human twins is specified by a complex interplay between intrauterine environmental and genetic factors, subject to tissue-specific influence

Lavinia Gordon,[1] Jihoon E. Joo,[2,3] Joseph E. Powell,[4,5] Miina Ollikainen,[6] Boris Novakovic,[2,3] Xin Li,[7] Roberta Andronikos,[3,7] Mark N. Cruickshank,[7] Karen N. Conneely,[8] Alicia K. Smith,[9] Reid S. Alisch,[10] Ruth Morley,[7] Peter M. Visscher,[4,5,11] Jeffrey M. Craig,[3,7,12,13] and Richard Saffery[2,3,12]

All DNA sequence identical ?
Other levels other 'genomes' ?

- Sequence itself: e.g. telomere length
- DNA content in mitochondria
- Epigenome
- Transcriptome
- Proteome
- Metabolome
- Connectome / node dynamics; routing
- Phenome (uni / multivariate): cell / person / group
- Environment
- Microbiome (a human body contains over 10 times more microbial than human cells)

*Dorret Boomsma*m Professor of Biological Psychology at VU University Amsterdam

J Clin Endocrinol Metab, 2010, 95(4):1909–1915

ORIGINAL ARTICLE

Endocrine Research

The Association of Mitochondrial Content with Prevalent and Incident Type 2 Diabetes

Erwin Reiling, Charlotte Ling, André G. Uitterlinden, Esther van't Riet, Laura M. C. Welschen, Claes Ladenvall, Peter Almgren, Valeriya Lyssenko, Giel Nijpels, Els C. van Hove, Johannes A. Maassen, Eco J. C. de Geus, Dorret I. Boomsma, Jacqueline M. Dekker, Leif Groop, Gonneke Willemsen,* and Leen M. 't Hart*

Heritability estimate in 212 twin-sib families

Sex, age, exercise, and BMI explain 4% of the variance in mtDNA content. Genetic modeling with these covariates yielded twin correlations of **0.34 for MZ** and **0.19 for DZ/sib pairs.** Heritability was estimated at 35%.

*Dorret Boomsma*m Professor of Biological Psychology at VU University Amsterdam

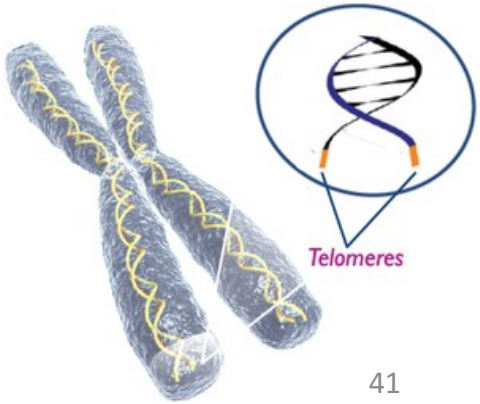
Meta-analysis of telomere length in 19,713 subjects

Linda Broer et al. (ENGAGE consortium) EJHG, 2013

	n	r	p-value
Siblings	1,553	0.49	$3.46*10^{-96}$
Monozygotic twins	2,534	**0.69**	0*
Dizygotic twins	1,940	**0.25**	$2.82*10^{-30}$
Spouses (<55)	962	0.20	$3.24*10^{-10}$
Spouses (>55)	977	0.31	$4.27*10^{-23}$

Heritability is ~70%

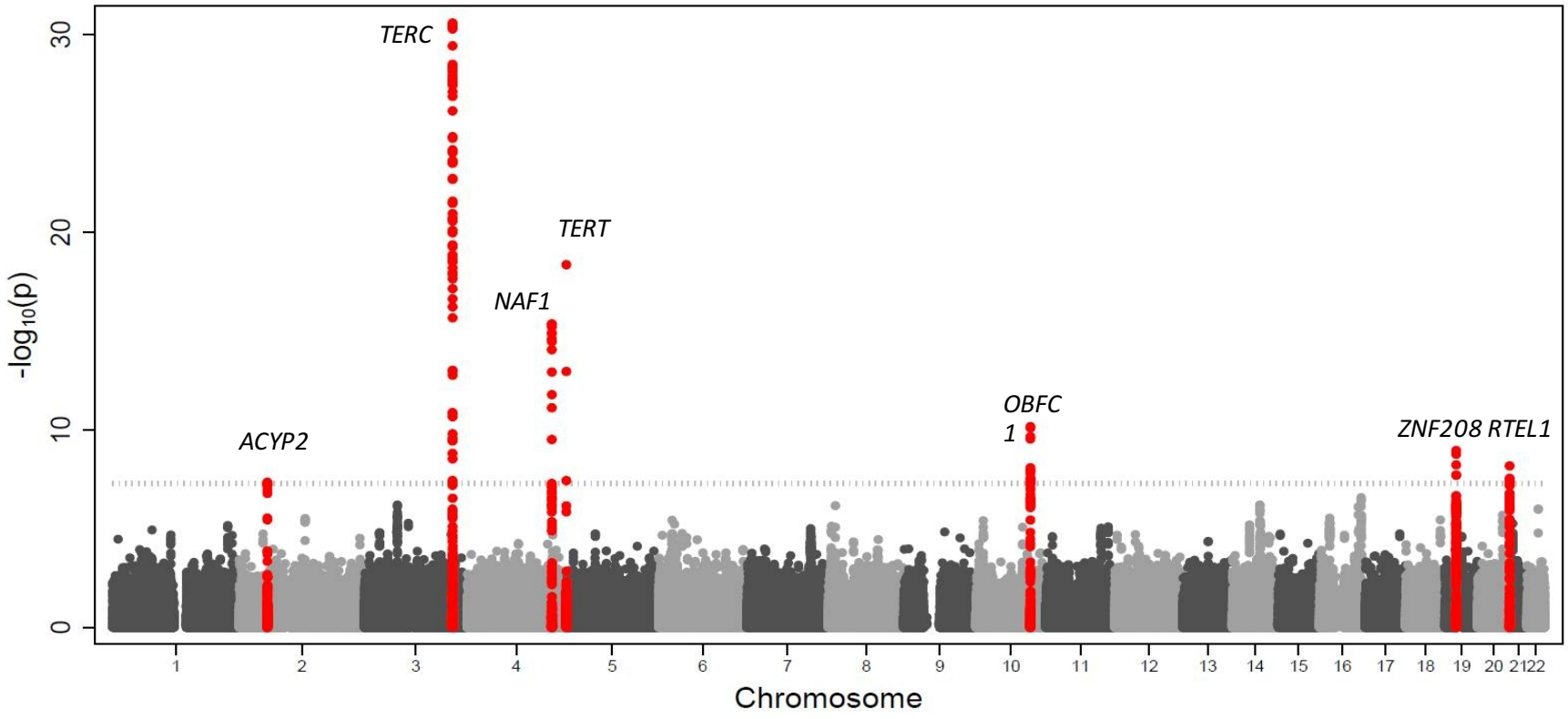
Parent offspring	n	r	p-value
Father-son	791	0.34	$2.57*10^{-23}$
Father-daughter	882	0.33	$3.99*10^{-24}$
Mother-son	850	0.42	$5.06*10^{-37}$
Mother-daughter	1,005	0.42	$2.99*10^{-45}$



Identification of seven loci affecting mean telomere length and their association with disease

Veryan Codd et al. (ENGAGE consortium) *NG*, 2013

Twin registries supplied 34% of samples



Microbiomes

ScienceTranslationalMedicine.org 21 May 2014

MICROBIOME

The Placenta Harbors a Unique Microbiome

Kjersti Aagaard,[1,2,3]* Jun Ma,[1,2] Kathleen M. Antony,[1] Radhika Ganu,[1] Joseph Petrosino,[4] James Versalovic[5]

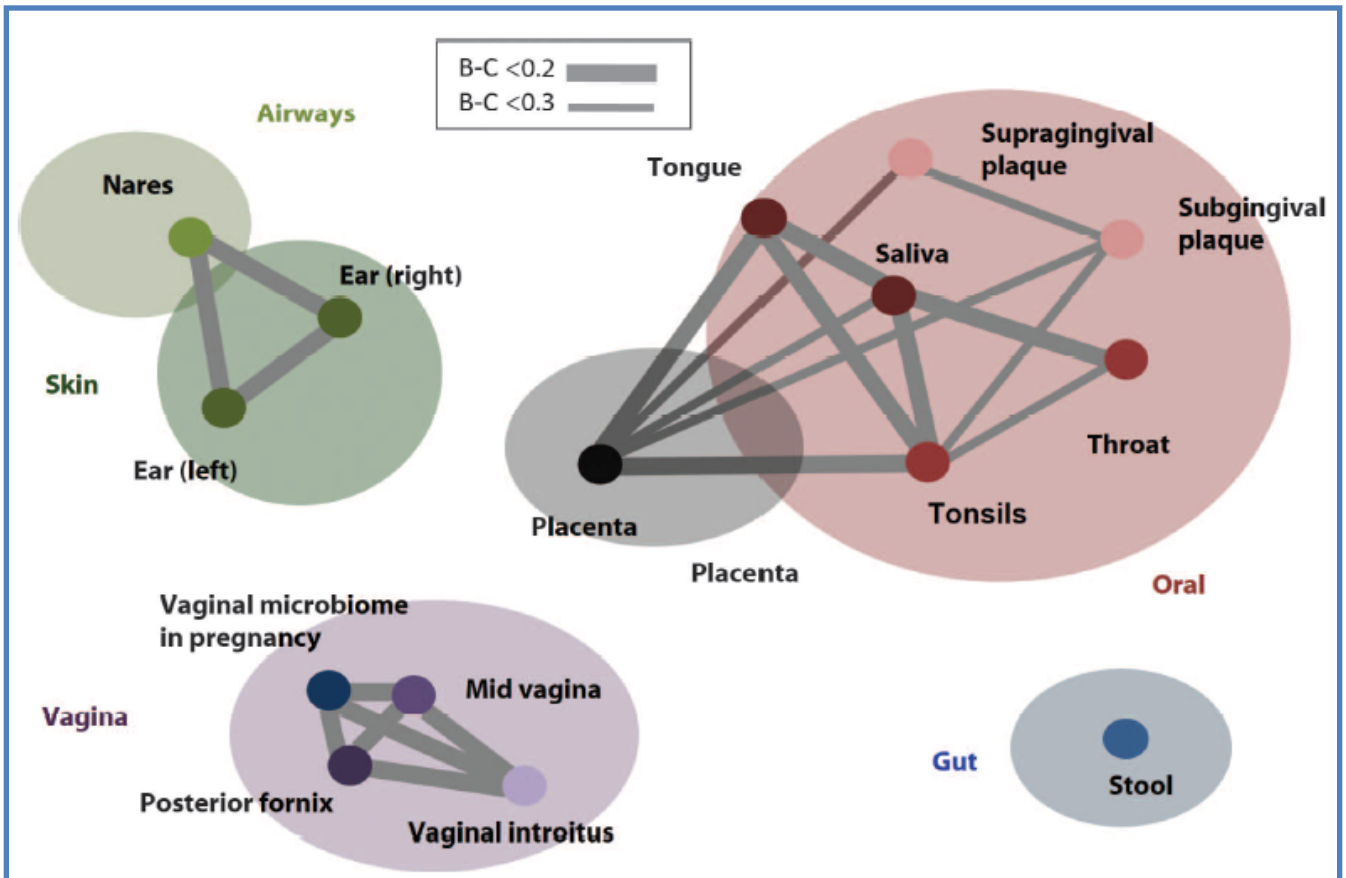
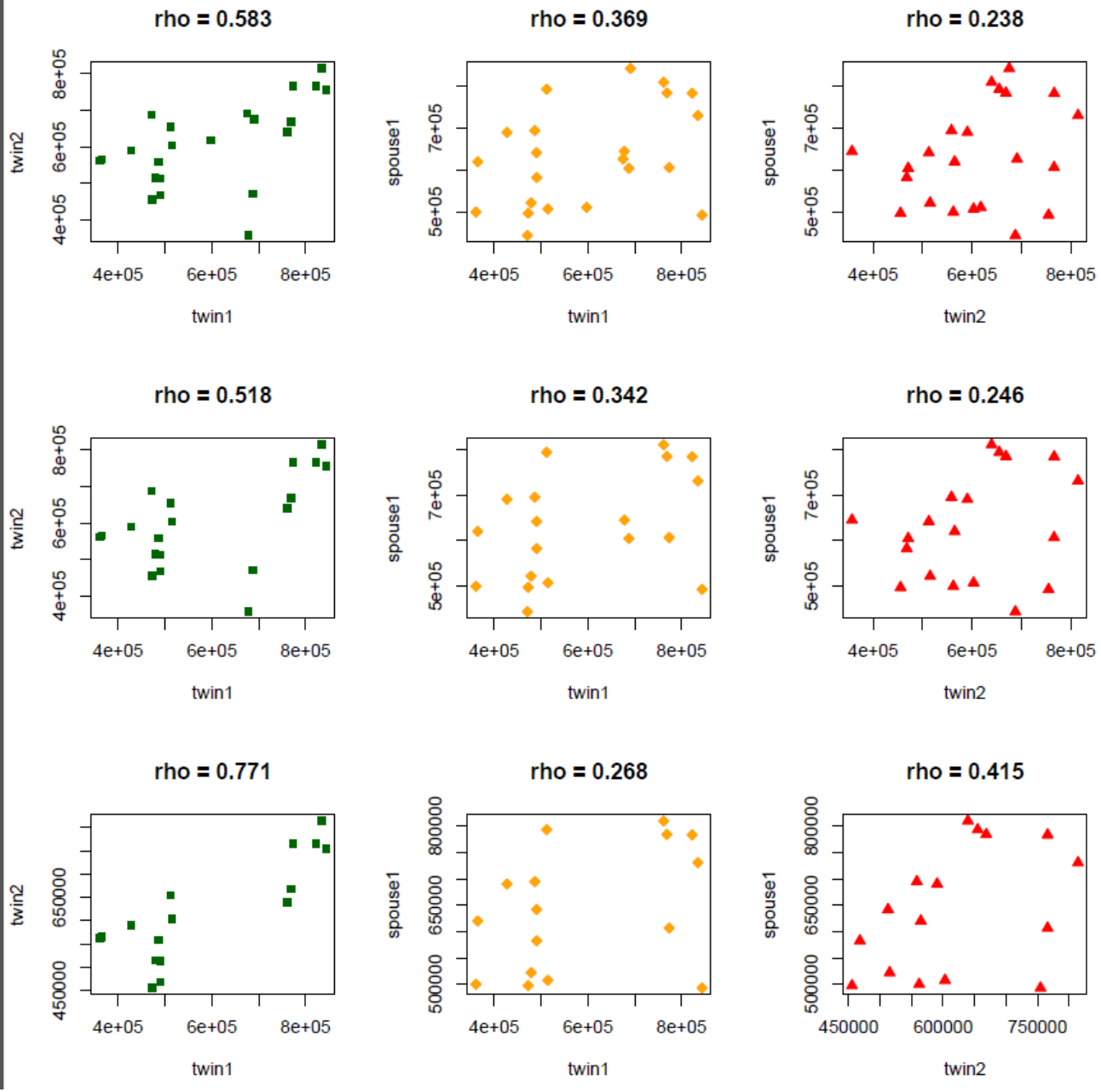


Fig. 1. The placental microbiome has a taxonomic profile that is similar to the oral microbiome.



- first row all trio's
- second row only those that are concordant for mode of birth
- the third those that are concordant and that are vaginally delivered

(a trio = 2 MZ twins + 1 spouse)

Article

Cell

Human Genetics Shape the Gut Microbiome

Julia K. Goodrich,[1,2] Jillian L. Waters,[1,2] Angela C. Poole,[1,2] Jessica L. Sutter,[1,2] Omry Koren,[1,2,7] Ran Blekhman,[1,8] Michelle Beaumont,[3] William Van Treuren,[4] Rob Knight,[4,5,6] Jordana T. Bell,[3] Timothy D. Spector,[3] Andrew G. Clark,[1] and Ruth E. Ley[1,2,*]

[1]Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY 14853, USA
[2]Department of Microbiology, Cornell University, Ithaca, NY 14853, USA
[3]Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, UK
[4]Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309, USA
[5]Biofrontiers Institute, University of Colorado, Boulder, CO 80309, USA
[6]Howard Hughes Medical Institute, University of Colorado, Boulder, CO 80309, USA
[7]Present address: Faculty of Medicine, Bar Ilan University, Safed 13115, Israel
[8]Present address: Department of Genetics, Cell Biology and Development, University of Minnesota, Minneapolis, MN 55455, USA
*Correspondence: rel222@cornell.edu
http://dx.doi.org/10.1016/j.cell.2014.09.053

*Dorret Boomsma*m Professor of Biological Psychology at VU University Amsterdam

Konkordancia: az ikerpárok hány %-a azonos az adott tulajdonság tekintetében.

Table 3 | **MZ and DZ twin concordance for complex disease**

	Probandwise concordance* (%)		Refs
	MZ twins	DZ twins	
Type 1 diabetes	42.9	7.4	129
Type 2 diabetes	34	16	130
Multiple sclerosis	25.3	5.4	149
Crohn's disease	38	2	150
Ulcerative colitis	15	8	150
Alzheimer's disease	32.2	8.7	134
Parkinson's disease	15.5	11.1	151
Schizophrenia	40.8	5.3	152
Major depression	31.1‡ or 47.6§	25.1‡ or 42.6§	153
Attention-deficit hyperactivity disorder	82.4	37.9	154
Autism spectrum disorders	93.7	46.7	155
Colorectal cancer	11	5	114
Breast cancer	13§	9§	114
Prostate cancer	18	3	114

STUDY DESIGNS

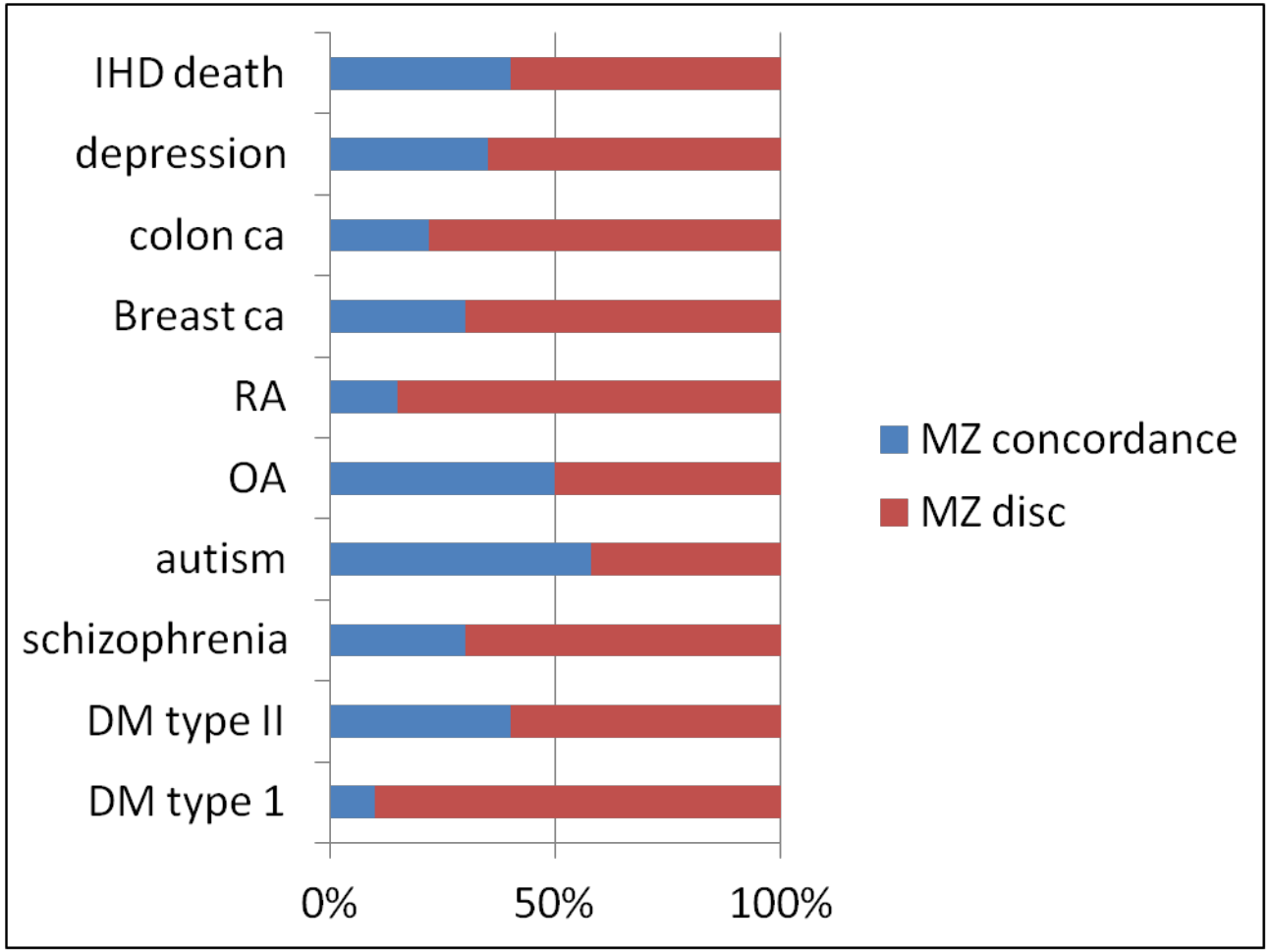
The continuing value of twin studies in the omics era

Jenny van Dongen[1], P. Eline Slagboom[2], Harmen H. M. Draisma[1], Nicholas G. Martin[3] and Dorret I. Boomsma[1]

van Dongen J. et al. (2012) The continuing value of twin studies in the omics era. Nature Reviews Genetics 13: 60–653

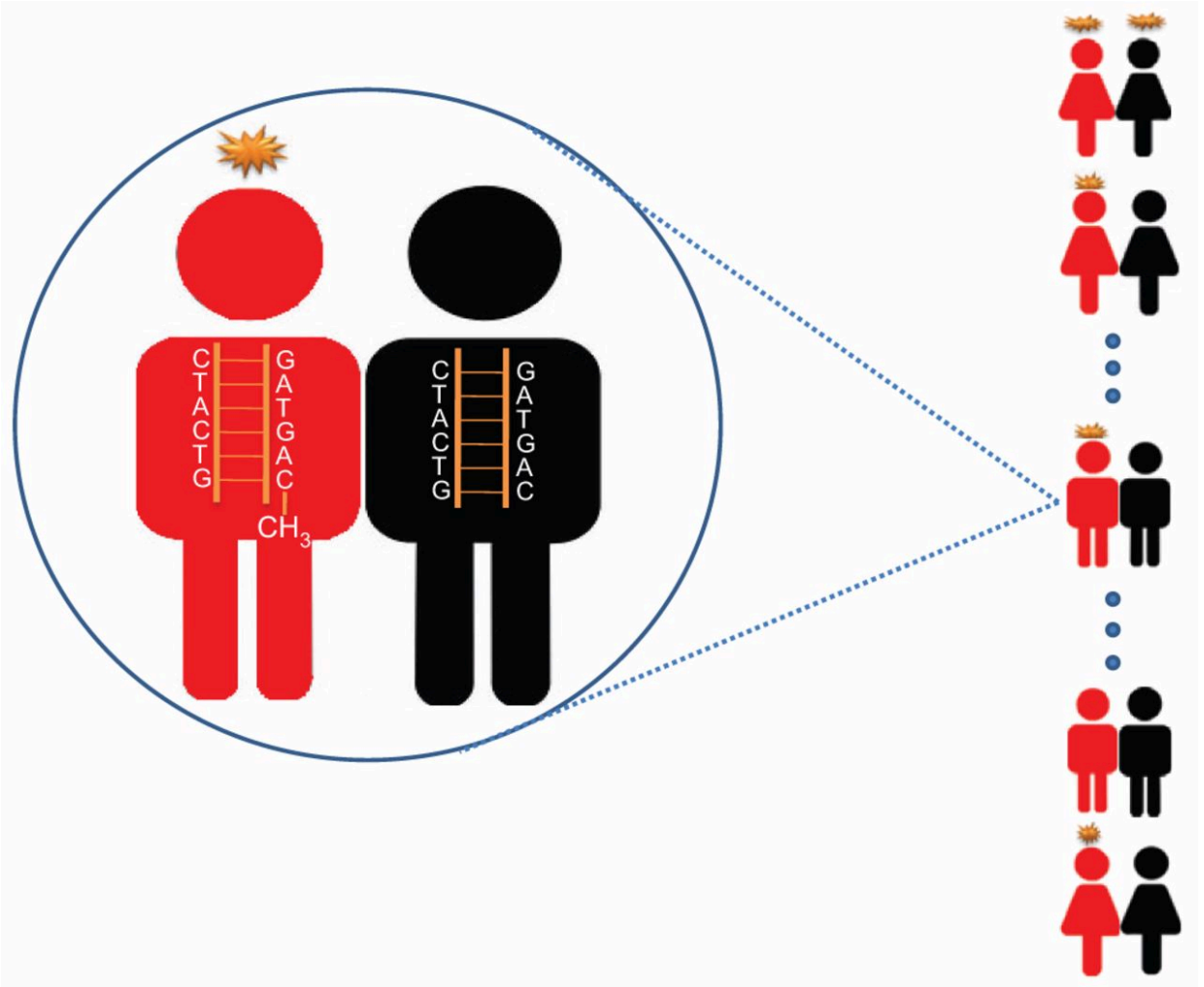
Identical but different-

low concordance rates for common disease in MZ twins



Tim Spector, Professor of Genetic Epidemiology at Kings College, London

The case co-twin design using identical twins discordant for a disease phenotype.



Qihua Tan et al. J Exp Biol 2015;218:134-139

Summary of epigenetic studies using MZ twin pairs discordant for disease or trait.

Table 1. Summary of epigenetic studies using MZ twin pairs discordant for disease or trait

Study	Year of publication	Sample size (pairs)	Coverage	Laboratory method	Statistical method	Discordant trait	Finding
Weksberg et al.	2002	10	*KCNQ1OT1* gene	Southern blotting	Descriptive	BWS	Loss of imprinting predisposes to BWS
Petronis et al.	2003	2	*DRD2* gene	Bis-seq	Descriptive	Schizophrenia	High epigenetic similarity in affected twins
Oates et al.	2006	1	*AXIN1* gene	Bis-seq	Descriptive	Caudal duplication	High methylation at promoter region of AXIN1 gene in affected twin
Mill et al.	2006	12	*COMT* gene	Bis-seq	Descriptive	Birth weight	Epigenetic variation in MZ twins may play a key role in the etiology of psychopathology
Kuratomi et al.	2008	1	Genome-wide	MS-RDA	Descriptive	Bipolar	Altered DNA methylation of PPIEL is associated with bipolar
Kaminsky et al.	2008	1	Genome-wide	Array	Descriptive	Risk-taking behaviour	Some DNA methylation differences may have developmental and behavioural implications
Mastroeni et al.	2009	1	Genome-wide	Immunohisto-chemistry	*t*-test	Alzheimer's disease	Low levels of DNA methylation observed in temporal neocortex neuronal nuclei of diseased twin
Javierre et al.	2010	5	Genome-wide	Array	Paired *t*-test	Systemic lupus erythematosus	Twin discordance is associated with widespread changes in DNA methylation
Baranzini et al.	2010	3	Genome-wide	Array	Descriptive	Multiple sclerosis	Very few changes in CpG methylation between siblings
Nguyen et al.	2010	3	Genome-wide	Array	SAM	Autism	Epigenetic contributions to autism confirmed
Harder et al.	2010	8	NF1 regions	Bis-seq	Paired *t*-test	NF1	DNA methylation of normal NF1 allele responsible for modification of NF1 phenotype.
Tierling et al.	2011	1	Candidate regions	Bis-seq	Descriptive	BWS	KvDMR1 was exclusively hypomethylated in all cell types of the affected BWS twin
Souren et al.	2011	8	Candidate regions	Bis-seq	Paired *t*-test	BMI	DNA methylation variability at nine regions does not contribute to discordancy in BMI
Dempster et al.	2011	22	Genome-wide	Infinium array	Paired *t*-test	Bipolar	Further evidence for DNA methylation in the etiology of major psychoses
Gervin et al.	2012	27	Genome-wide	Infinium array	Paired *t*-test	Psoriasis	Epigenetic alteration potentially contributes to the development of psoriasis
Runyon et al.	2012	21	Selected loci	Bis-seq	Paired *t*-test	Asthma	Differential function of T cell subsets is regulated by changes in DNA methylation
Souren et al.	2013	17	Genome-wide	Infinium array	Rank test	Birth weight	No distinguishable genome-wide DNA methylation differences due to birth weight discordance
Wong et al.	2014	50	Genome-wide	Infinium array	Paired *t*-test	Autism	Numerous differentially methylated regions associated with autism

MZ, monozygotic; BWS, Beckwith–Wiedemann syndrome; NF1, neurofibromatosis type 1.

Qihua Tan et al. J Exp Biol 2015;218:134-139

HONNAN TUDHATÓ, HOGY EGY BETEGSÉG ÖRÖKLŐDŐ VAGY SEM?

Családi halmozódás

PROBLÉMÁK
A CSALÁDI HALMOZÓDÁS
ÉRTÉKELÉSÉBEN

Az emberek nemcsak génjeiket, hanem a környezetüket is átadják gyermekeiknek.

Nehéz megkülönböztetni ezeket.

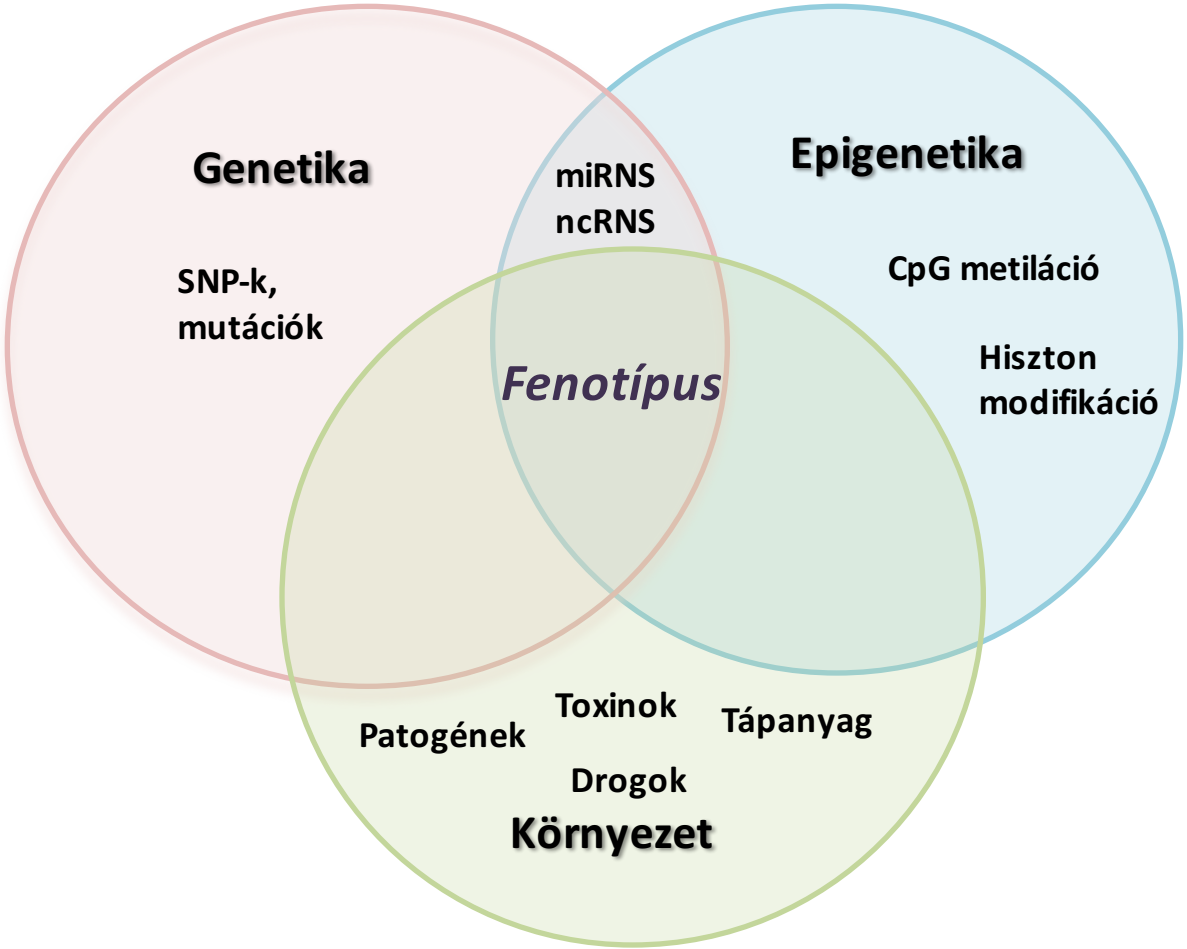
Iker vizsgálatok

Örökbefogadottak vizsgálata

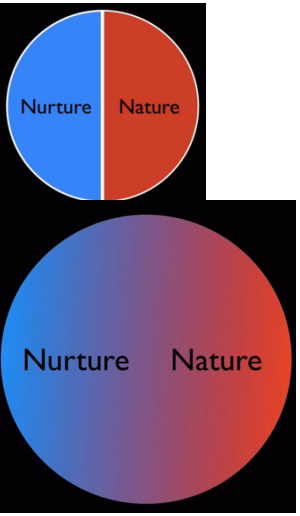
„memetika”

Dr .Falus András ábrája alapján

Öröklés vagy Környezet?



Régebben:



Nature.com Kidney International 79, 23-32 (January (1) 2011) | doi:10.1038/ki.2010.335

Genetika („hardver”)- epigenetika („szoftver”)

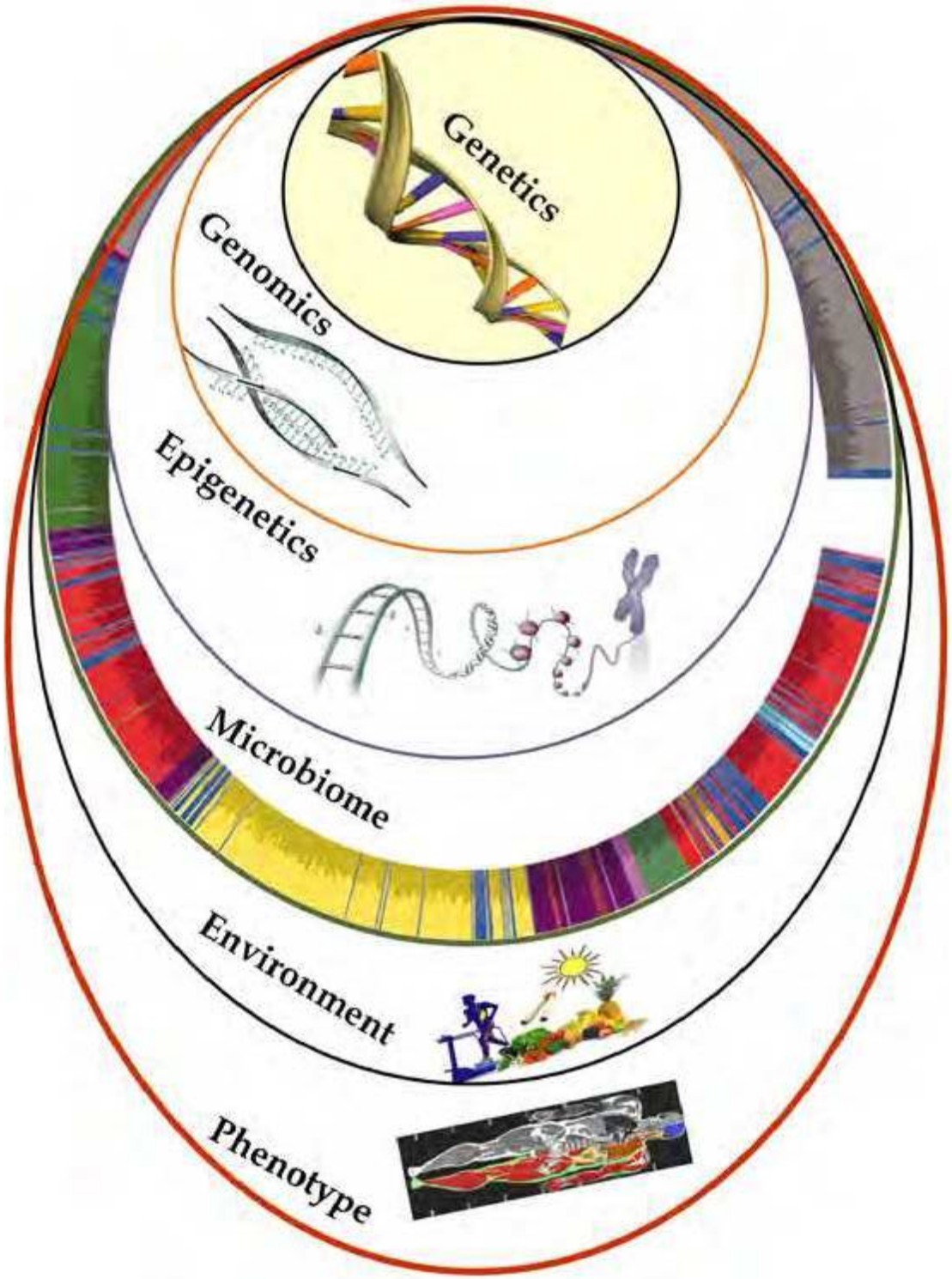
- Az öröklődés (hajlam) lényegében **irreverzibilis**
- Az epigenetikai hatások nagy része **reverzibilis,**

✓**tehát változtathatunk rajta!**

Az ÉLETMÓD jelentősége!!!

TESTI-LELKI EGÉSZSÉG

Dr. Falus András ábrája alapján


Genetics
Genomics
Epigenetics
Microbiome
Environment
Phenotype

One-Year Mission & Twins Study

Human Research

https://www.nasa.gov/content/twins-study

The Twins Study is unique demonstration research to further NASA's use of personalized medicine.

- Research techniques used in personalized medicine (technologies such as genetic sequencing) are employed to discern individual responses to the spaceflight environment
- Research from the molecular level to whole body function to brain function is being integrated together into one, coordinated study

The Twins Study is multi-faceted national cooperation between universities, corporations, and government laboratory expertise.

- 10 individual investigations
- 12 universities
- NASA biomedical laboratories
- National Space Biomedical Research Institute Consortium

Twins Study | The Research

1. Human Physiology

These investigations will look at how the spaceflight environment may induce changes in different organs like the heart, muscles or brain.

- Metabolomic and Genomic Markers of Atherosclerosis as Related to Oxidative Stress, Inflammation, and Vascular Function in Twin Astronauts

- Proteomic Assessment of Fluid Shifts and Association with Visual Impairment and Intracranial Pressure in Twin Astronauts

2. Behavioral Health

This investigation will help characterize the effects spaceflight may have on perception and reasoning, decision making and alertness.

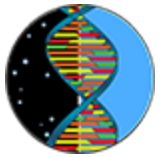
- Cognition on Monozygotic Twin on Earth

http://www.nasa.gov/twins-study/reseach

3. Microbiology/Microbiome

This investigation will explore the brothers' dietary differences and stressors to find out how both affect the organisms in the twins' guts.

- Metagenomic Sequencing of the Microbiome in GI Tract of Twin Astronauts



4. Molecular/Omics

These investigations will look at the way genes in the cells are turned on and off as a result of spaceflight; and how stressors like radiation, confinement and microgravity prompt changes in the proteins and metabolites gathered in biological samples like blood, saliva, urine and stool.

- Differential Effects on Telomeres and Telomerase in Twin Astronauts Associated With Spaceflight
- Comprehensive Whole Genome Analysis of Differential Epigenetic Effects of Space Travel on Monozygotic Twins
- Biochemical Profile: Homozygous Twin control for a 12 month Space Flight Exposure
- The Landscape of DNA and RNA Methylation Before, During, and After Human Space Travel
- Longitudinal Integrated Multi-Omics Analysis of the Biomolecular Effects of Space Travel
- Characterizing Personalized Changes in Baseline Immune Abnormalities and Stimulated Immune Response in the Presence of a Benign Trivalent, Inactivated, Flu Vaccination

1. Functional

These investigations will examine the changes in crew member performance of functional tasks after 12 months in a low-gravity environment: Field Test and Functional Task Test.

2. Behavioral Health

These investigations will examine psychological effects of long-duration spaceflight on crew members by conducting cognition tests, neuromapping studies, sleep monitoring, journaling analyses and a reaction self-test.

3. Visual Impairment

These investigations will examine ocular health and the body's response to fluid shifts in a weightless environment. This includes examining techniques to measure intracranial pressure.

4. Metabolic

These investigations will examine integrated immune, salivary markers, biochemical profiles and the relationship between biological markers of oxidative and inflammatory stress and the risk for atherosclerosis in a long-duration, weightless environment. An integrated immune monitoring strategy also will be validated.

5. Physical Performance

These investigations will examine exercise capability with a focus on physical performance of bone, muscle and the cardiovascular system over time in a weightless environment: Sprint Study and Hip QCT Study.

6. Microbial

These investigations will examine changes in the microbiome of crewmembers.

7. Human Factors

These investigations will examine how astronauts interact with their environment aboard the International Space Station focusing on fine motor performance, habitability, and training retention.

http://www.nasa.gov/1ym/research

Köszönöm szépen a figyelmet!

Melicher Dóra

ügyvezető
EDUVITAL NET Nonprofit Egészségnevelési Társaság
+36 (20) 421 7215
dora.melicher@eduvital.net

Értsd, Csináld, Szeresd!

PhD hallgató
Molekuláris Orvostudományok Doktori Iskola
SE Genetikai, Sejt- és Immunbiológiai Tanszék
melicher.dora@med.semmelweis-univ.hu

munkatárs, kutató
Magyar Ikrerregiszter
Hungarian Twin Registry
www.ikrek.hu