Ο ρόλος της Μοριακής Βιολογίας στην εμφάνιση & εξέλιξη των χρόνιων νοσημάτων

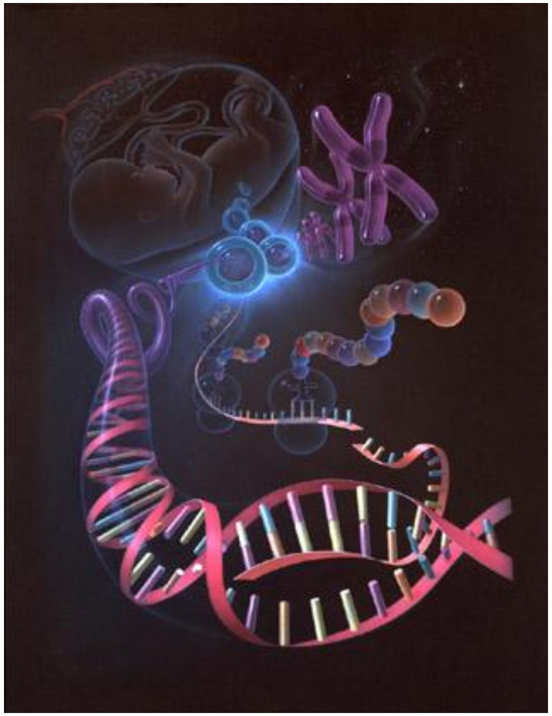
Π.Γ.ΧΑΛΒΑΤΣΙΩΤΗΣ

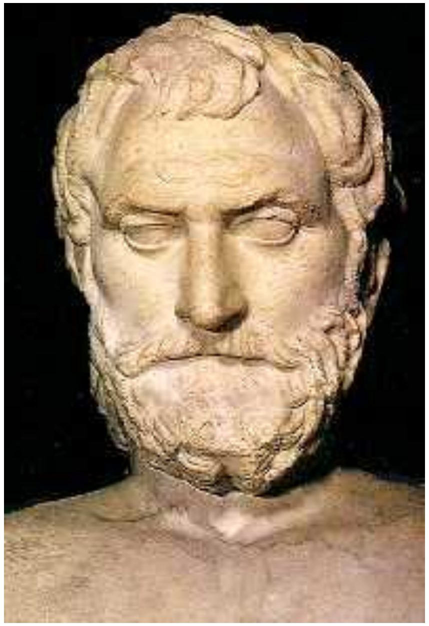
Β' ΠΡΟΠΑΙΔΕΥΤΙΚΗ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ – ΜΟΝΑΔΑ ΕΡΕΥΝΑΣ & ΔΙΑΒΗΤΟΛΟΓΙΚΟ ΚΕΝΤΡΟ ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΑΘΗΝΩΝ

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝ.ΝΟΣΟΚΟΜΕΙΟ "ΑΤΤΙΚΟΝ"

Δεν υπάρχει σύγκρουση συμφερόντων

«THE GENE» HYPOTHESIS

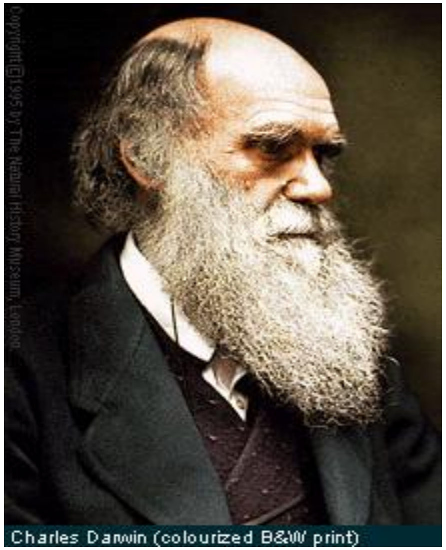




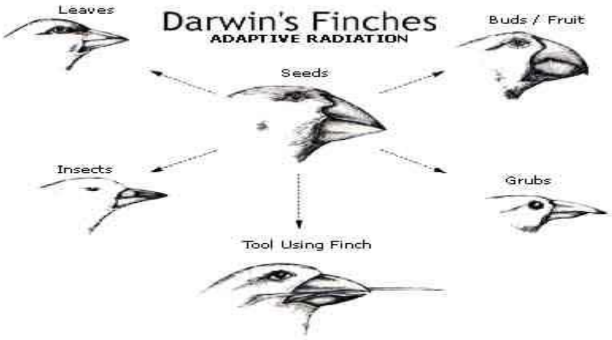
ANAXAGORAS
(500 - 428 B.C.)

ANAXIMANDROS
(611-546 B.C.)

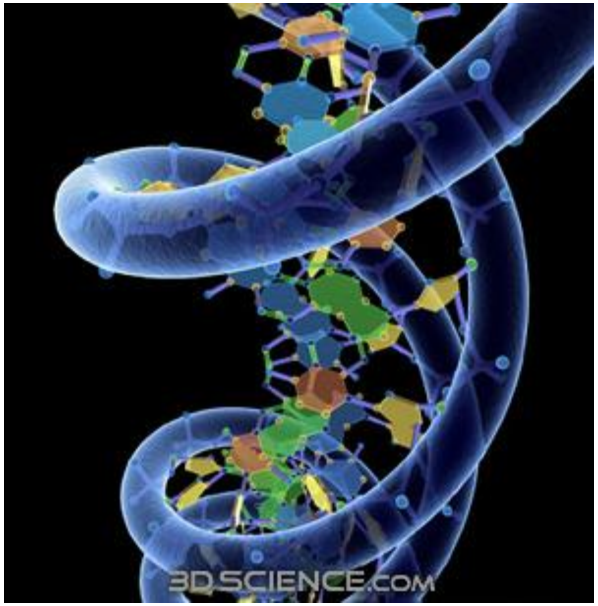
From the 20th .....
.....to the 21st century



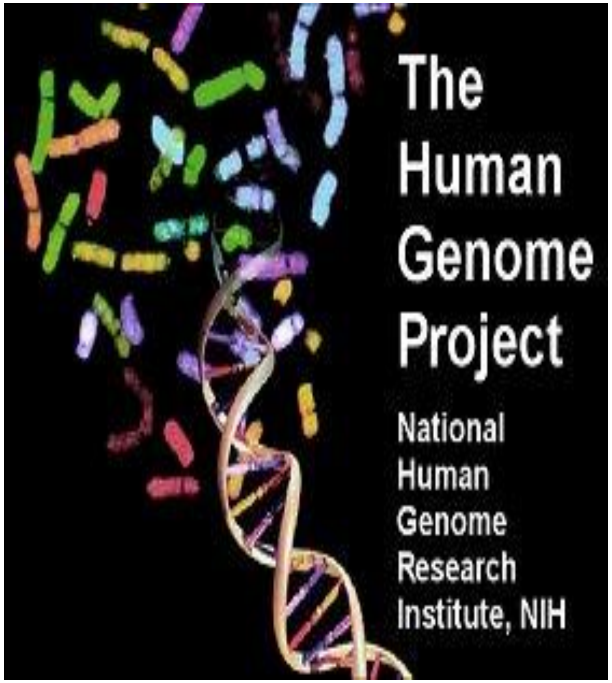
1809 - 1882



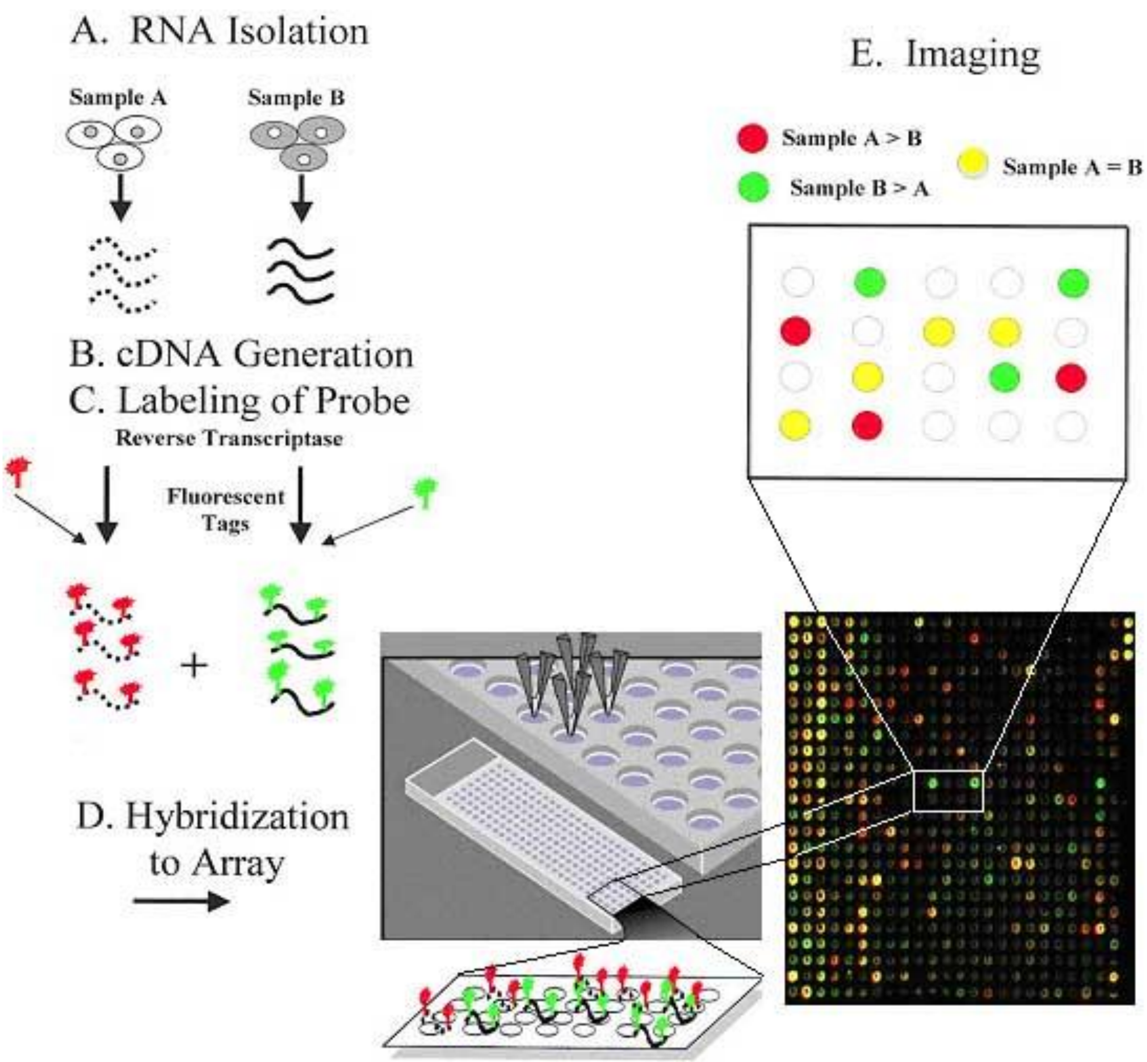
April 1953

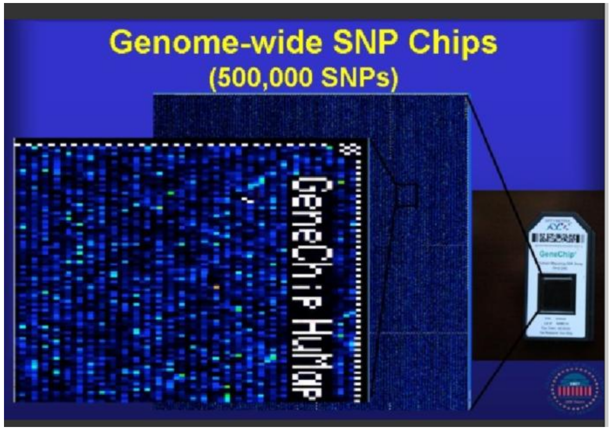


April 2003

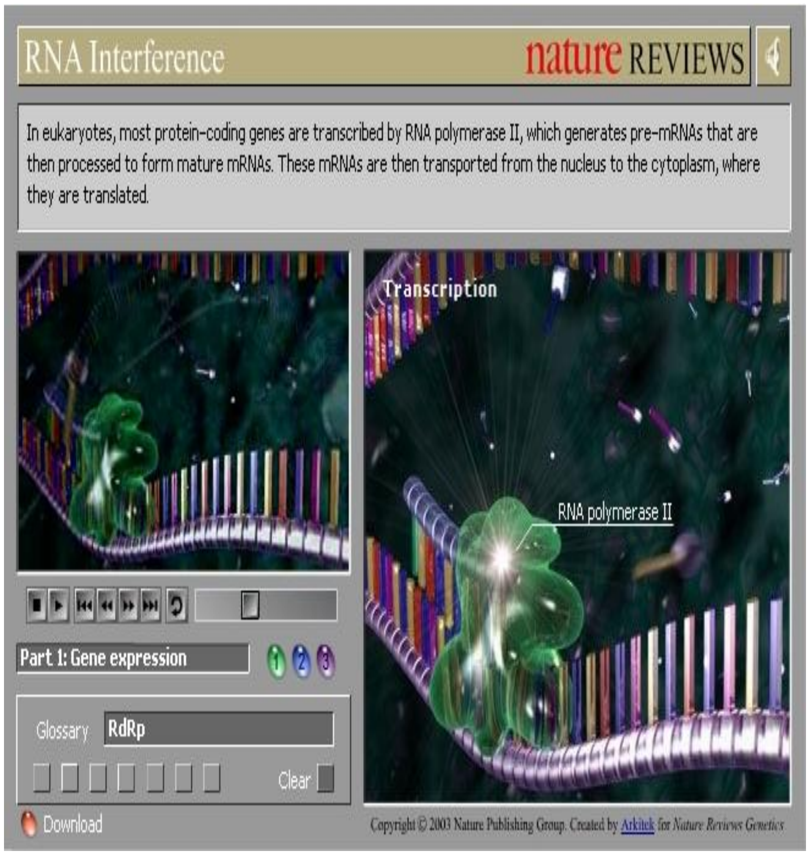


MICROARRAYS
GENE PROJECTS





GENE EXPRESSION IN DIABETES MELLITUS



- **Studied 6.451 genes where hyperglycemia modified the expression of 85**
- **Insulin treatment normalized 74**
- **…while modified the expression of 29, previously normal .!!!**
- **But 11 remained unchanged**

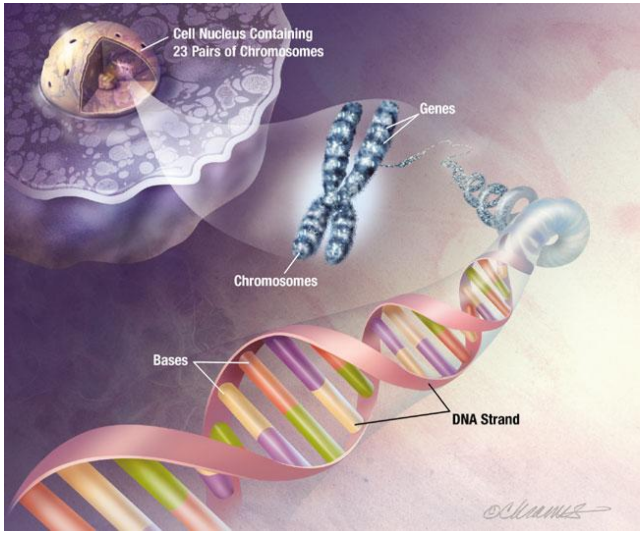
Sreekumar R, Halvatsiotis P, Nair S. Diabetes 51:1913-20, 2002

GENOME & DIABETES MELLITUS

Fold	Gene name
Structural/contractile genes	
2.9*	Calmodulin Type I
2.1*	Troponin I fast-twitch
2.1	Troponin C fast-twitch
2.0*	Skeletal muscle C-protein
2.0	Troponin I slow-twitch
1.9	Tropomyosin
Stress response/energy metabolism	
3.2	Heat shock protein, 70 kDa
2.0	NADH dehydrogenase-ubiquinone
Growth factor/tissue development	
2.9	IGFBP-5
2.2*	MCL1
2.1*	Cadherin FIB3

Gene Expression Profile in Skeletal Muscle of Type 2 Diabetes and the Effect of Insulin Treatment

Raghavakaimal Sreekumar, Panagiotis Halvatsiotis, et al *Diabetes* 51:1913-1920, 2002



«DIABETOGENIC» GENES

Type 2 Diabetes (T2D): "The geneticist's nightmare"

- Family history as a substantial risk factor
  - But relative risk to a sibling is only ~3.5
- Environment as a major contributor
- Family linkage studies relatively disappointing
- Validated genes prior to 2007:
  - *PPARG* (candidate gene)
  - *KCNJ11* (candidate gene)
  - *TCF7L2* (linkage study)

Three Groups Working Together

\# cases + controls

FUSION

S1: 1161 + 1174

S2: 1215 + 1258

DGI

S1: 1464 + 1467

S2: 5065 + 5785

WTCCC/UKT2D

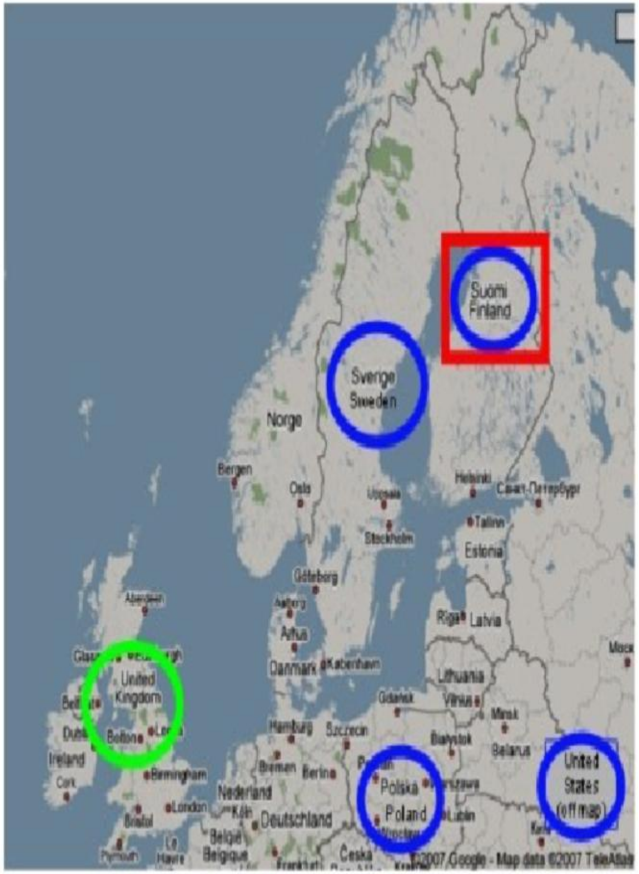
S1: 1924 + 2938

S2: 3757 + 5346

Totals

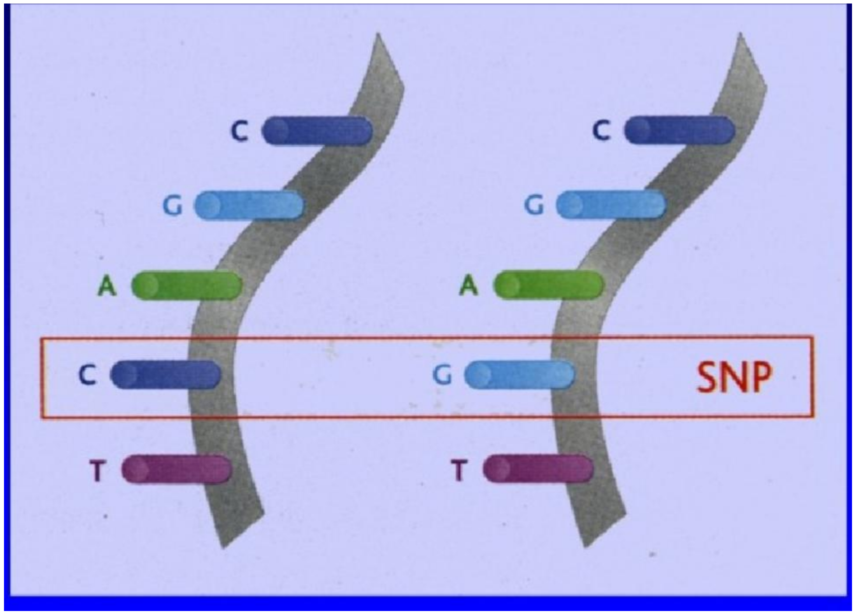
S1 = 4549 + 5579

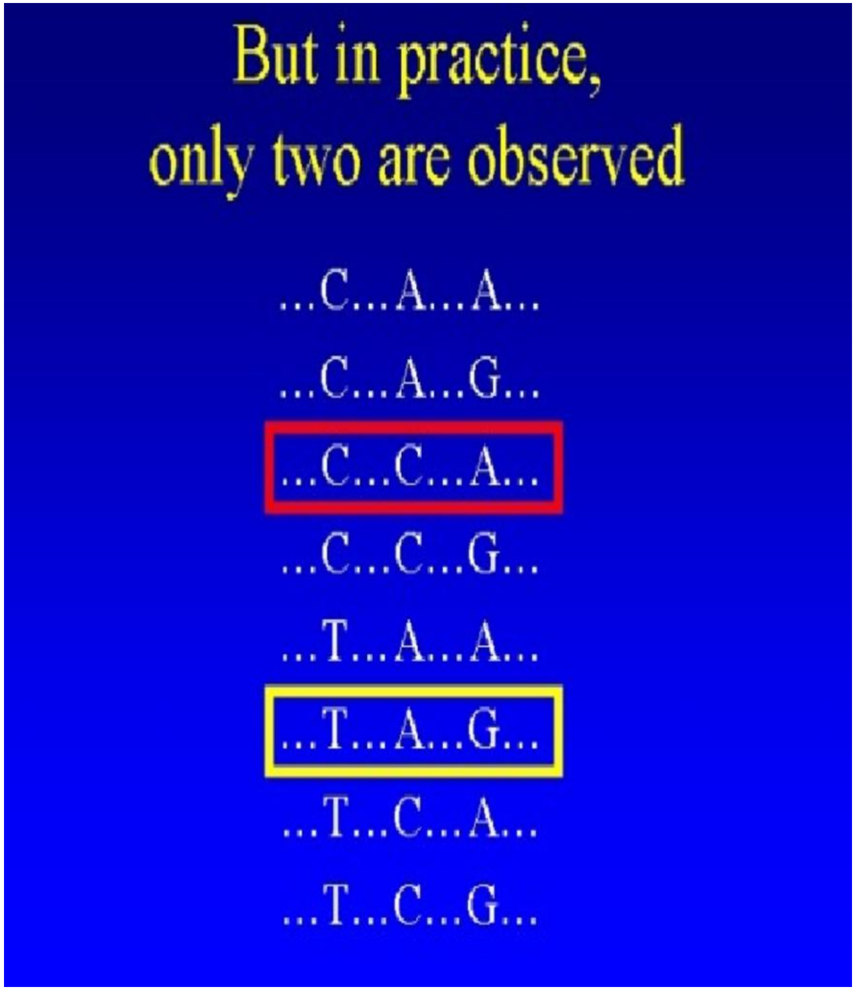
S2 = 10053 + 12389



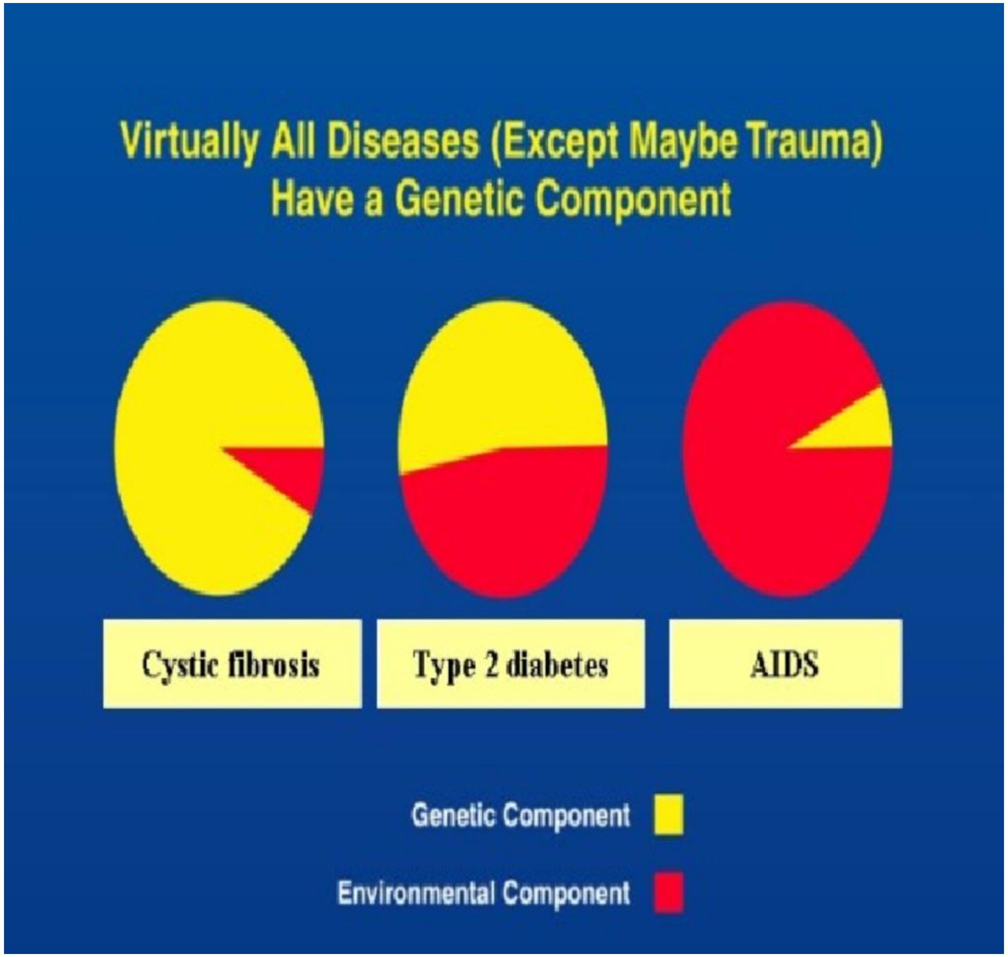
(n=32,554)

SINGLE NUCLEOTIDE POLYMORPHISM

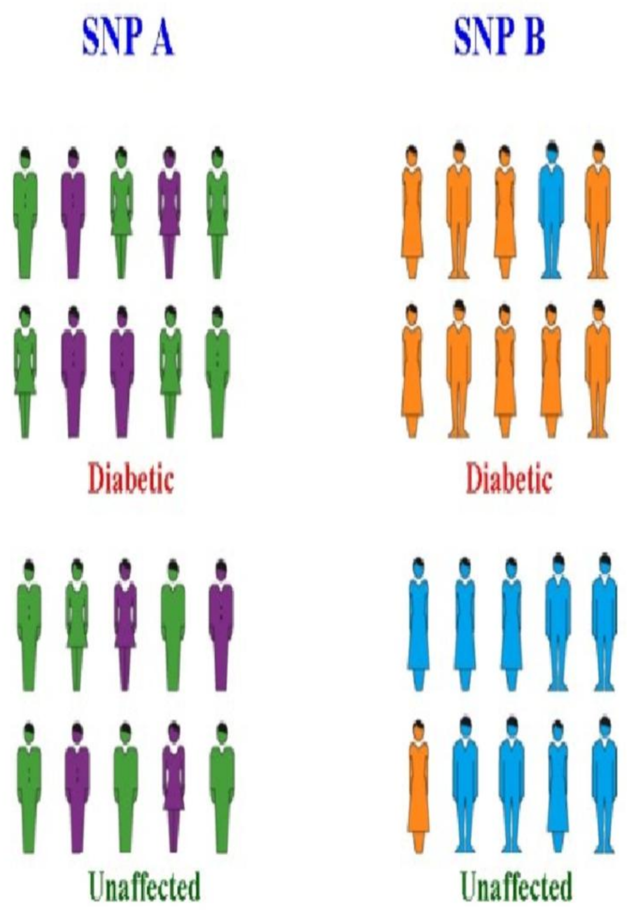




HAPLOTYPES



Virtually All Diseases (Except Maybe Trauma)
Have a Genetic Component
Cystic fibrosis
Type 2 diabetes
AIDS
Genetic Component
Environmental Component

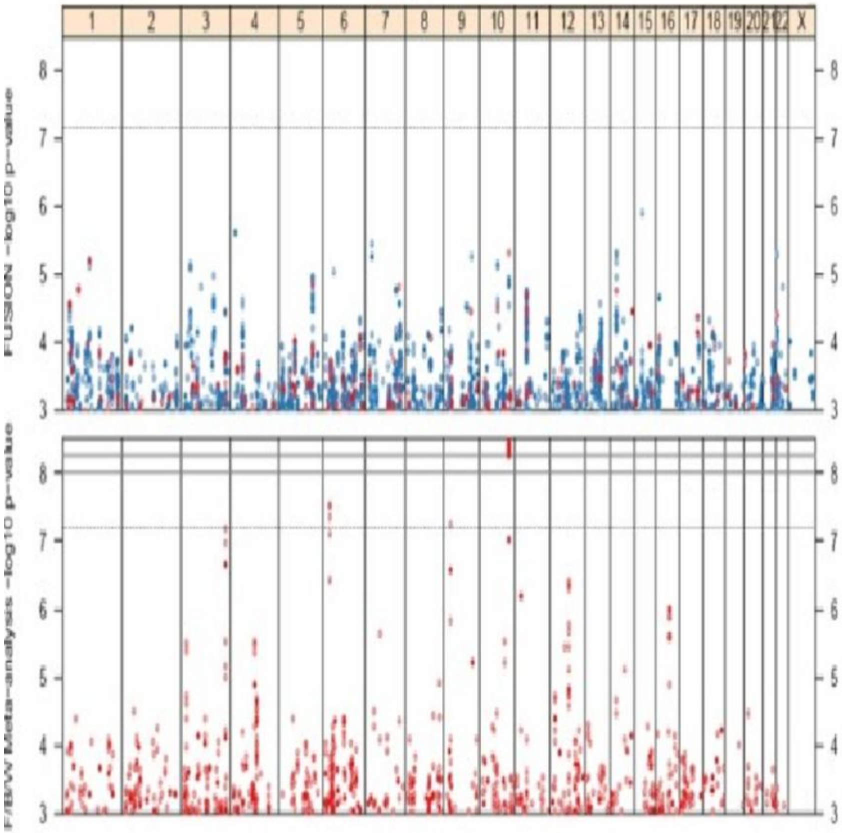


SNP A
SNP B
Diabetic
Diabetic
Unaffected
Unaffected

«DIABETOGENIC» GENES

Results of GWA with 317,503 SNPs

Stage 1: FUSION only (1161 cases + 1174 controls)



Stage 1 – FUSION + DGI + WTCCC

(4549 cases + 5579 controls)

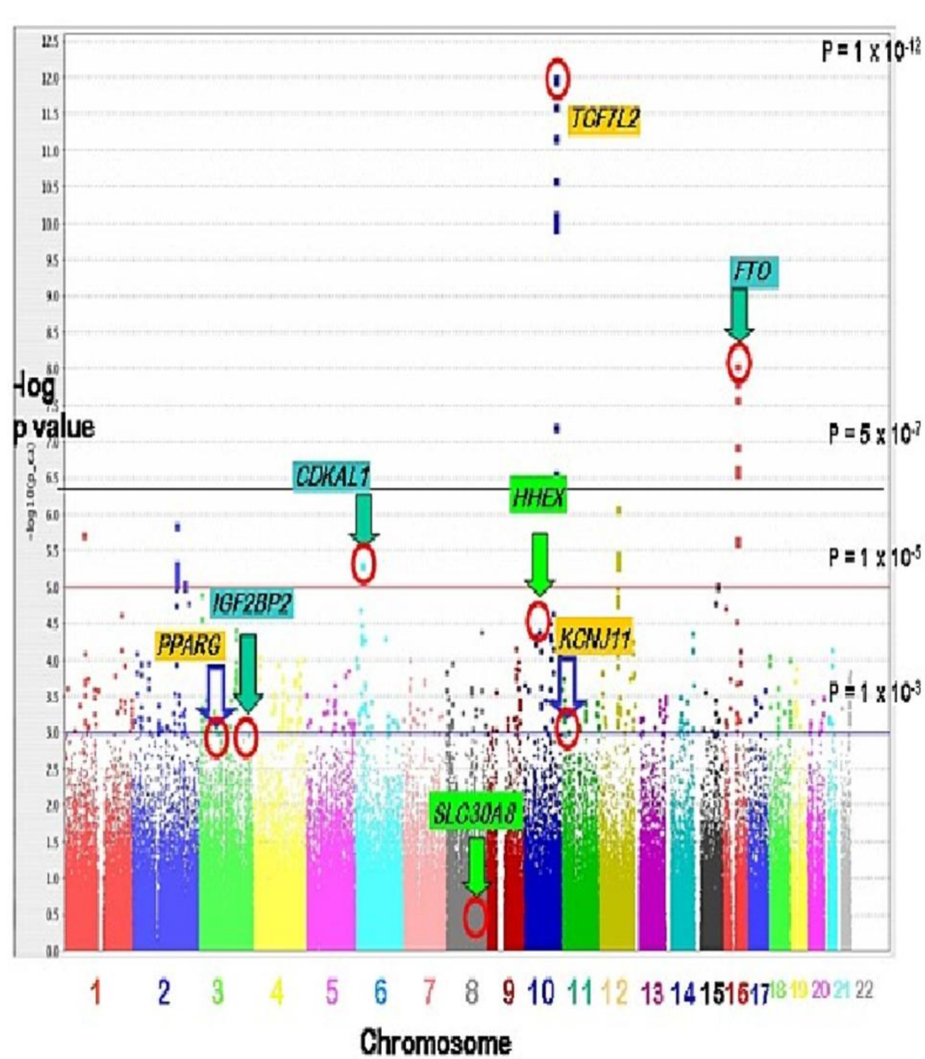
Top 10 Results From Combined Analysis

n = 32,554

	FUSION		DGI		WTCCC/UKT2D		All Samples	
Gene	OR	p-value	OR	p-value	OR	p-value	OR	p-value
TCF7L2	1.34	1.3×10^{-8}	1.38	2.3×10^{-31}	1.37	6.7×10^{-13}	1.37	1.0×10^{-48}
IGF2BP2	1.18	2.1×10^{-4}	1.17	1.7×10^{-9}	1.11	1.6×10^{-4}	1.14	8.9×10^{-16}
CDKN2A/B	1.20	.0022	1.20	5.4×10^{-8}	1.19	4.9×10^{-7}	1.20	7.8×10^{-15}
FTO	1.11	0.016	1.03	0.25	1.23	7.3×10^{-14}	1.17	1.3×10^{-12}
CDKAL1	1.12	0.0095	1.08	0.0024	1.16	1.3×10^{-8}	1.12	4.1×10^{-11}
KCNJ11	1.11	0.013	1.15	1.0×10^{-7}	1.15	0.0013	1.14	6.7×10^{-11}
HHEX	1.10	0.026	1.14	1.7×10^{-4}	1.13	4.6×10^{-6}	1.13	5.7×10^{-10}
SLC30A8	1.18	7.0×10^{-5}	1.07	0.047	1.12	7.0×10^{-5}	1.12	5.3×10^{-8}
Chr 11	1.48	5.7×10^{-8}	1.16	0.12	1.13	0.068	1.23	4.3×10^{-7}
PPARG	1.20	0.0014	1.09	0.019	1.23	0.0013	1.14	1.7×10^{-6}

TCF7L2

- Type 2 susceptibility gene (linkage study in Iceland)
- Widely replicated in type 2 diabetes
- Caucasians and Africans, lower in Asian

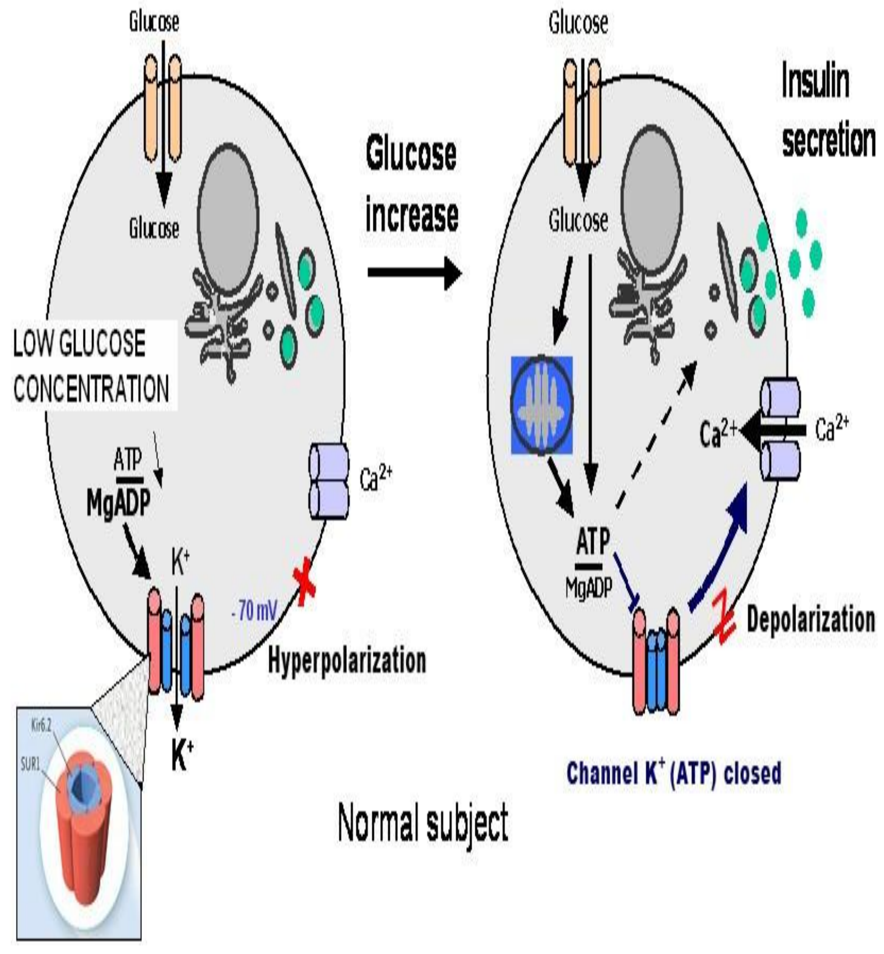


KCNJ11

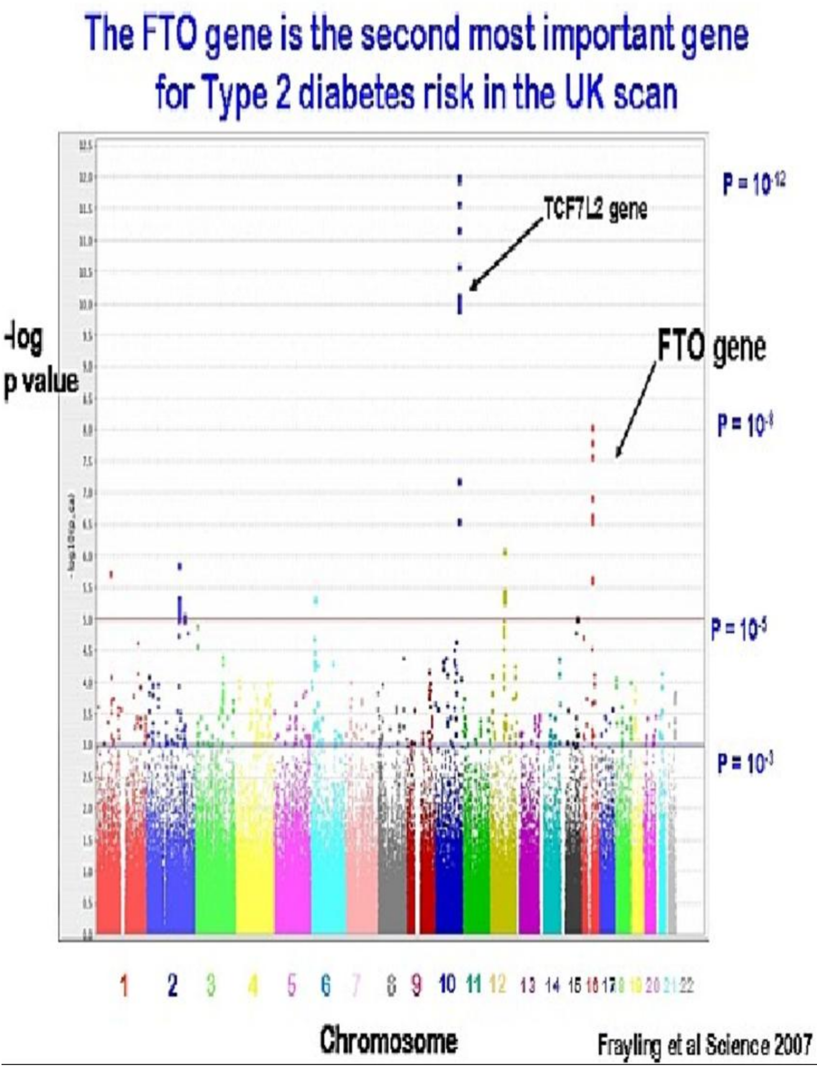
Defected insulin secretion

Coding of Kir6.2 subunit, in ***ATP- sensitive K⁺*** channels

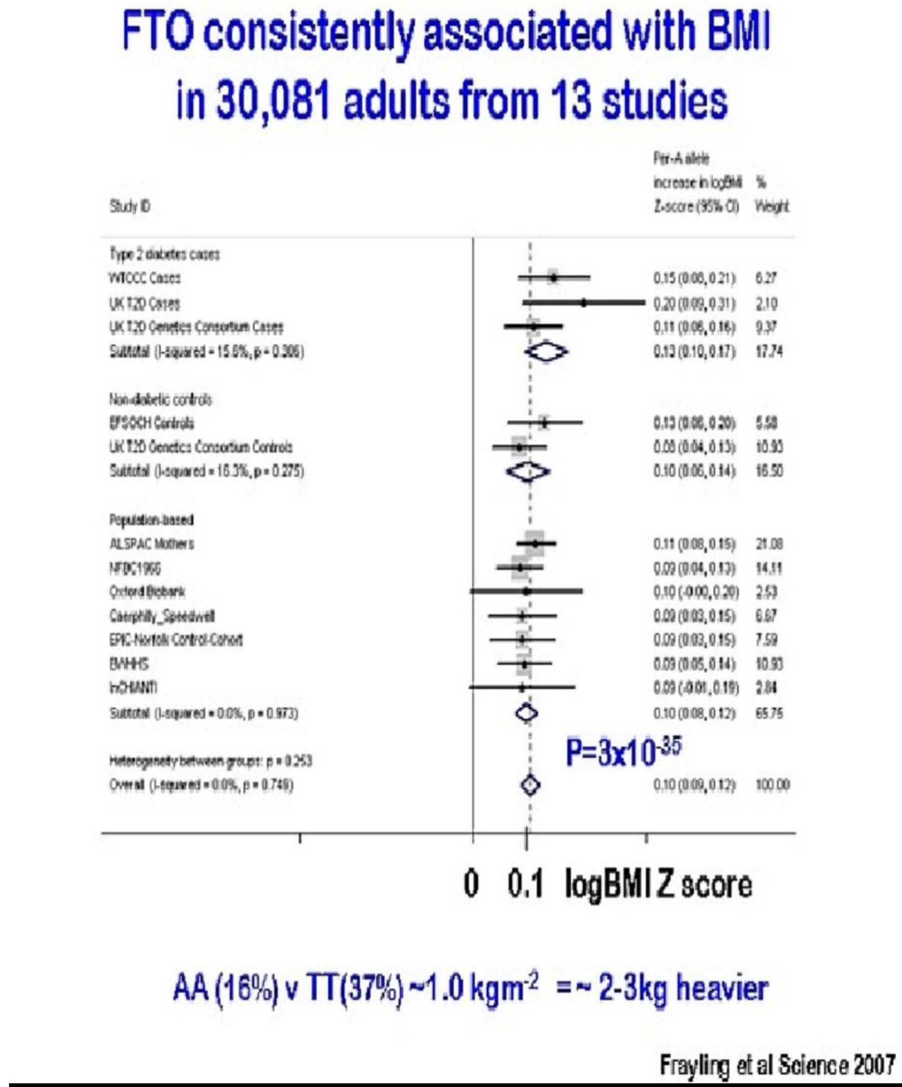
(ages <6 mo)



FTO GENE



The FTO gene is the second most important gene for Type 2 diabetes risk in the UK scan
-log p value
P = 10-12
TCF7L2 gene
FTO gene
P = 10-8
P = 10-5
P = 10-3
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome
Frayling et al Science 2007



FTO consistently associated with BMI in 30,081 adults from 13 studies
Study ID
Per-A allele increase in logBMI Z-score (95% CI)
% Weight
Type 2 diabetes cases
WTCCC Cases 0.15 (0.08, 0.21) 6.27
UK T2D Cases 0.20 (0.09, 0.31) 2.10
UK T2D Genetics Consortium Cases 0.11 (0.06, 0.16) 9.37
Subtotal (I-squared = 15.6%, p = 0.306) 0.13 (0.10, 0.17) 17.74
Non-diabetic controls
EFSOCH Controls 0.13 (0.06, 0.20) 5.58
UK T2D Genetics Consortium Controls 0.08 (0.04, 0.13) 10.93
Subtotal (I-squared = 16.3%, p = 0.275) 0.10 (0.06, 0.14) 16.50
Population-based
ALSPAC Mothers 0.11 (0.08, 0.15) 21.08
NFBC1966 0.09 (0.04, 0.13) 14.11
Oxford Biobank 0.10 (-0.00, 0.20) 2.53
Caerphilly_Speedwell 0.09 (0.03, 0.15) 6.67
EPIC-Norfolk Control-Cohort 0.09 (0.03, 0.15) 7.59
BWHHS 0.09 (0.05, 0.14) 10.93
InCHIANTI 0.09 (-0.01, 0.19) 2.84
Subtotal (I-squared = 0.0%, p = 0.973) 0.10 (0.08, 0.12) 65.75
Heterogeneity between groups: p = 0.253
Overall (I-squared = 0.0%, p = 0.749) 0.10 (0.09, 0.12) 100.00
P=3x10-35
0 0.1 logBMI Z score
AA (16%) v TT(37%) ~1.0 kgm-2 =~ 2-3kg heavier
Frayling et al Science 2007

CDKN2A/B
& CARDIOVASCULAR DISEASE

Sciencexpress Report

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,[1*†] Alexander Pertsemlidis,[2*] Nihan Kavaslar,[1] Alexandre Stewart,[1] Robert Roberts,[1] David R. Cox,[3] David A. Hinds,[3] Len A. Pennacchio,[4] Anne Tybjaerg-Hansen,[5] Aaron R. Folsom,[6] Eric Boerwinkle,[7] Helen H. Hobbs,[2,8] Jonathan C. Cohen[2,8†]

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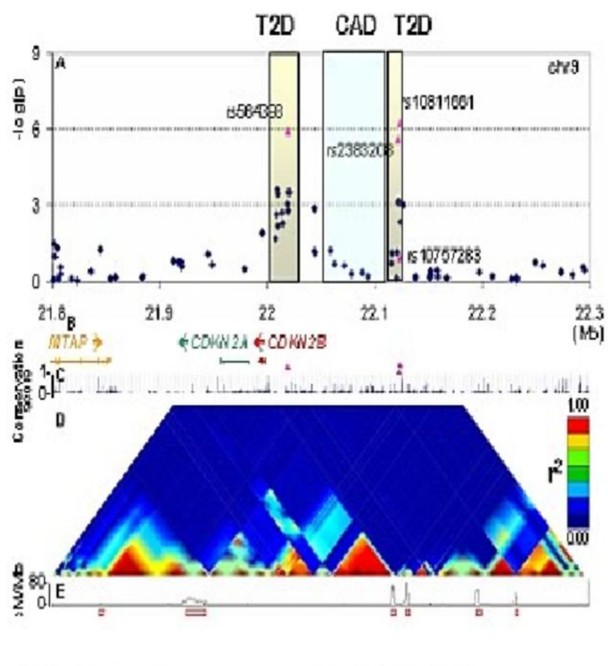
Sciencexpress Report

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,[1*] Gudmar Thorleifsson,[1*] Andrei Manolescu,[1*] Solveig Gretarsdottir,[1] Thorarinn Blondal,[1] Aslaug Jonasdottir,[1] Adalbjorg Jonasdottir,[1] Asgeir Sigurdsson,[1] Adam Baker,[1] Arnar Palsson,[1] Gisli Masson,[1] Daniel Gudbjartsson,[1] Kristinn P. Magnusson,[1] Karl Andersen,[2] Allan I. Levey,[3] Valgerdur M. Backman,[1] Sigurborg Matthiasdottir,[1] Thorbjorg Jonsdottir,[1] Stefan Palsson,[1] Helga Einarsdottir,[1] Steinunn Gunnarsdottir,[1] Arnaldur Gylfason,[1] Viola Vaccarino,[3] W. Craig Hooper,[3] Muredach P. Reilly,[4] Christopher B. Granger,[5] Harland Austin,[3] Daniel J Rader,[4] Svati H. Shah,[5] Arshed A. Quyyumi,[3] Jeffrey R. Gulcher,[1] Gudmundur Thorgeirsson,[1] Unnur Thorsteinsdottir,[1] Augustine Kong,[1†] Kari Stefansson[1†]

Type 2 diabetes and CAD map to adjacent haplotypes close to CDKN2A/2B



Chr9 signal maps near *CDKN2A/N2B* genes

	OR	p
WTCCC	1.22 (1.09-1.37)	7.6×10^{-4}
UK rep	1.16 (1.08-1.28)	1.7×10^{-4}
DGI	1.20 (1.12-1.28)	5.4×10^{-8}
FUSION	1.20 (1.07-1.30)	2.2×10^{-6}
All	1.20 (1.14-1.25)	7.8×10^{-15}

	OR	p
WTCCC	1.16 (1.07-1.27)	3.2×10^{-4}
UK rep	1.12 (1.05-1.19)	8.6×10^{-4}
DGI	1.05 (0.94-1.17)	0.6
FUSION	1.13 (1.01-1.27)	0.04
all	1.12 (1.07-1.17)	1.2×10^{-7}

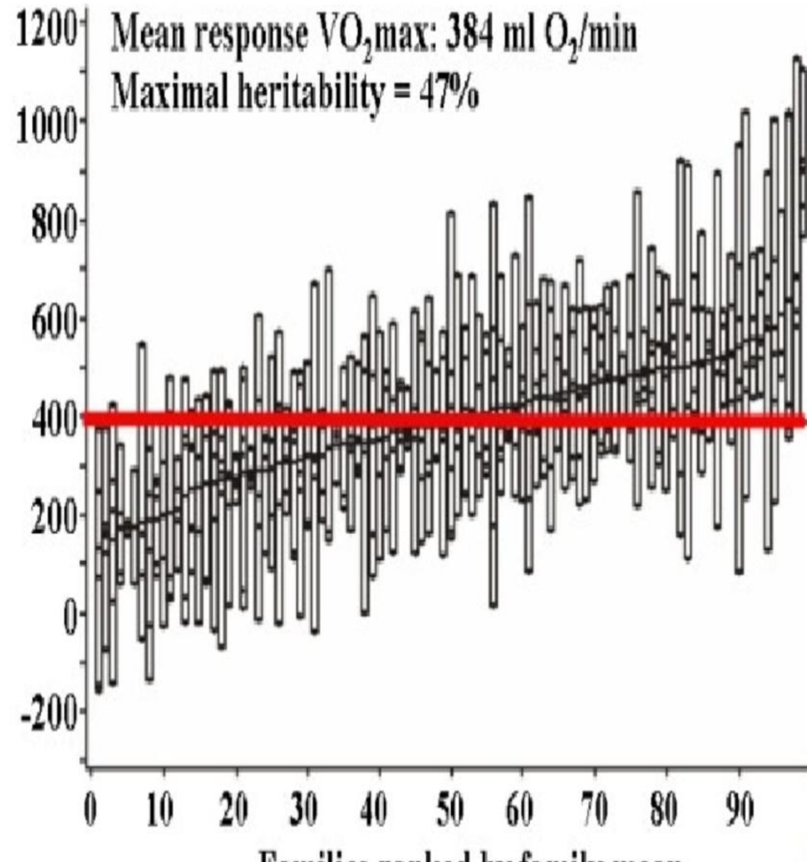
Zeggini et al Science 2007 & WTCCC Nature 2007

HERITAGE FAMILY STUDY

The HERITAGE Family Study Exercise Training Program

- Duration: 20 weeks
- Frequency: 3 times per week
- Intensity and duration:
  - Wks 1-2: HR at 55% VO_{2max} for 30 min
  - Wks 3-14: gradually to HR at 75% max, 50 min
  - Wks 15-20: HR at 75% VO_{2max} for 50 min
- Computer-controlled cycle ergometers
- Training supervised in the laboratory

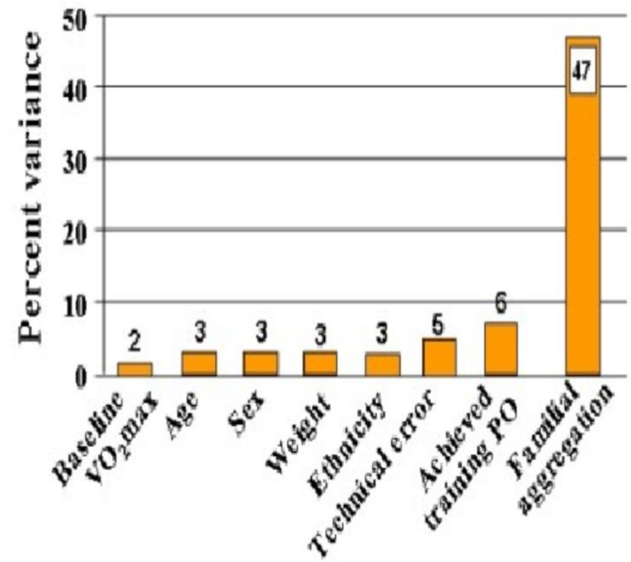
VO_2max Response in Whites of HFS



Bouchard et al, JAP, 1999

ΑΠΟΔΟΣΗ ΣΤΗΝ ΑΣΚΗΣΗ

VO_2max Training Response in HFS

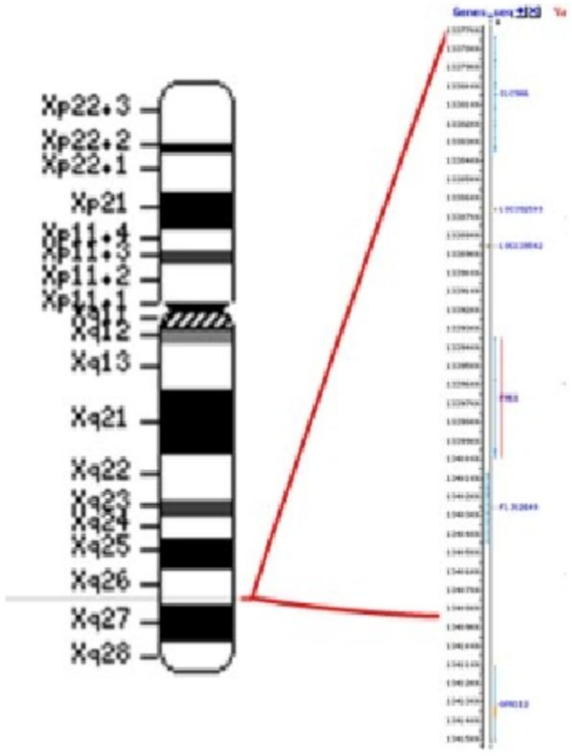


483 Whites, 259 Blacks, 17-65 years of age;
Mean gain = 384 ml O_2, SD > 202 ml

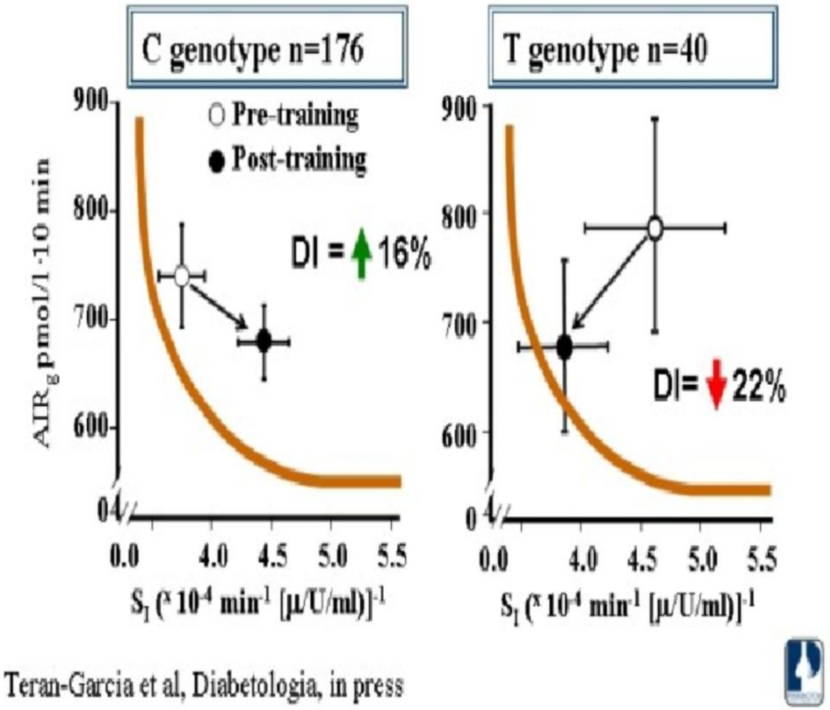
Bouchard et al, JAP, 1999

ΑΣΚΗΣΗ - ΓΟΝΙΔΙΑΚΟ ΥΠΟΣΤΡΩΜΑ & ΙΝΣΟΥΛΙΝΙΚΗ ΕΥΑΙΣΘΗΣΙΑ

FHL1 is Encoded on Chr X p27

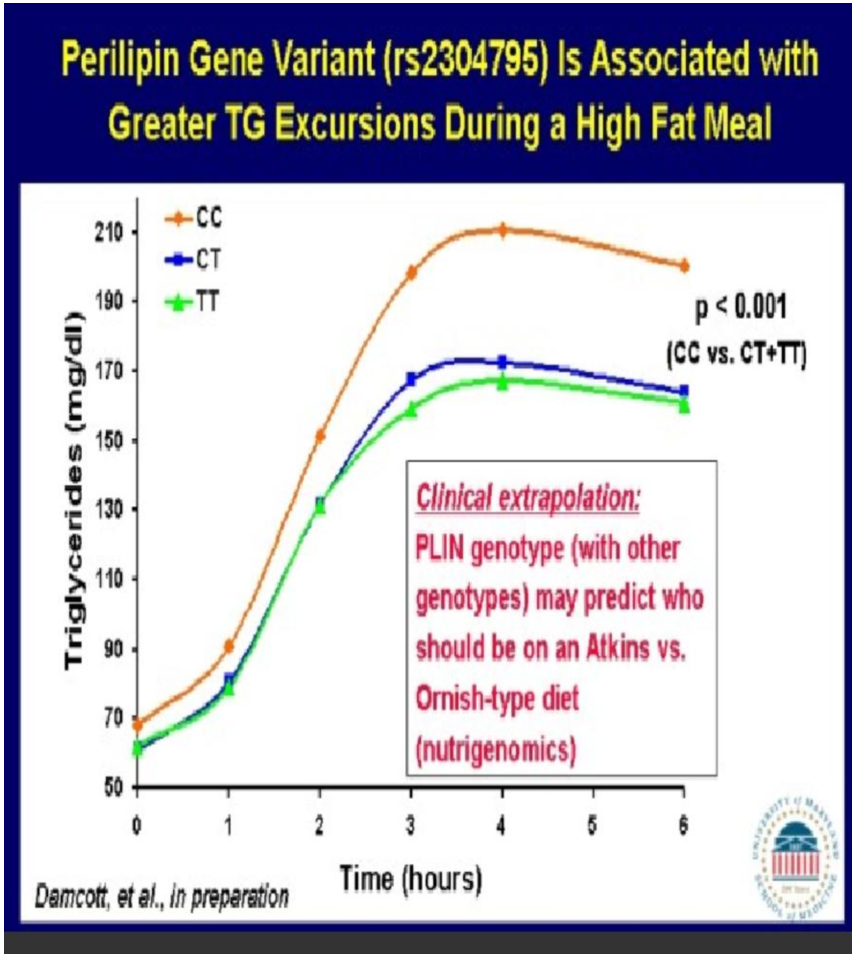


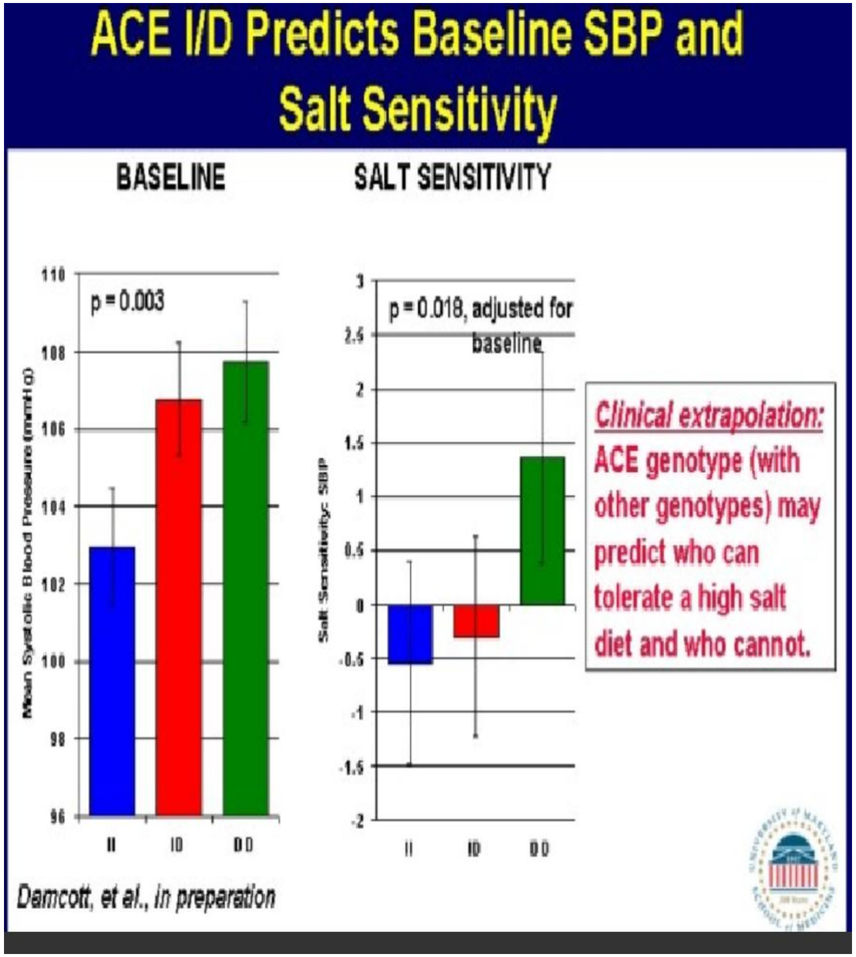
Pre- and Post-training Effects for White Males of HFS with FHL1 rs2180062C>T



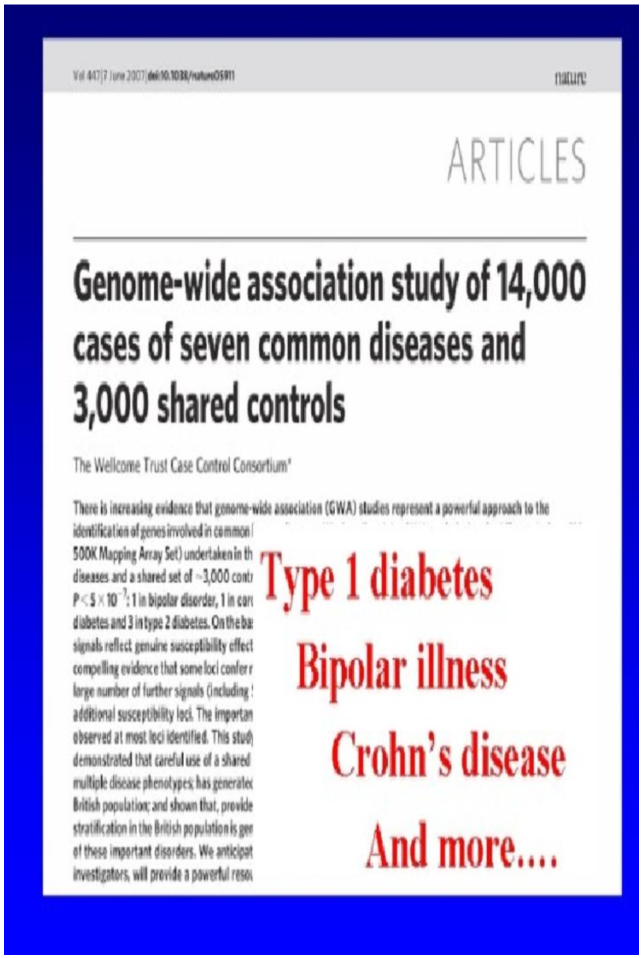
Teran-Garcia et al, Diabetologia, in press

ΜΕΤΑΒΟΛΙΚΕΣ ΠΑΡΑΜΕΤΡΟΙ & ΑΠΛΟΤΥΠΟΙ





COMMON GENETIC BACKGROUND



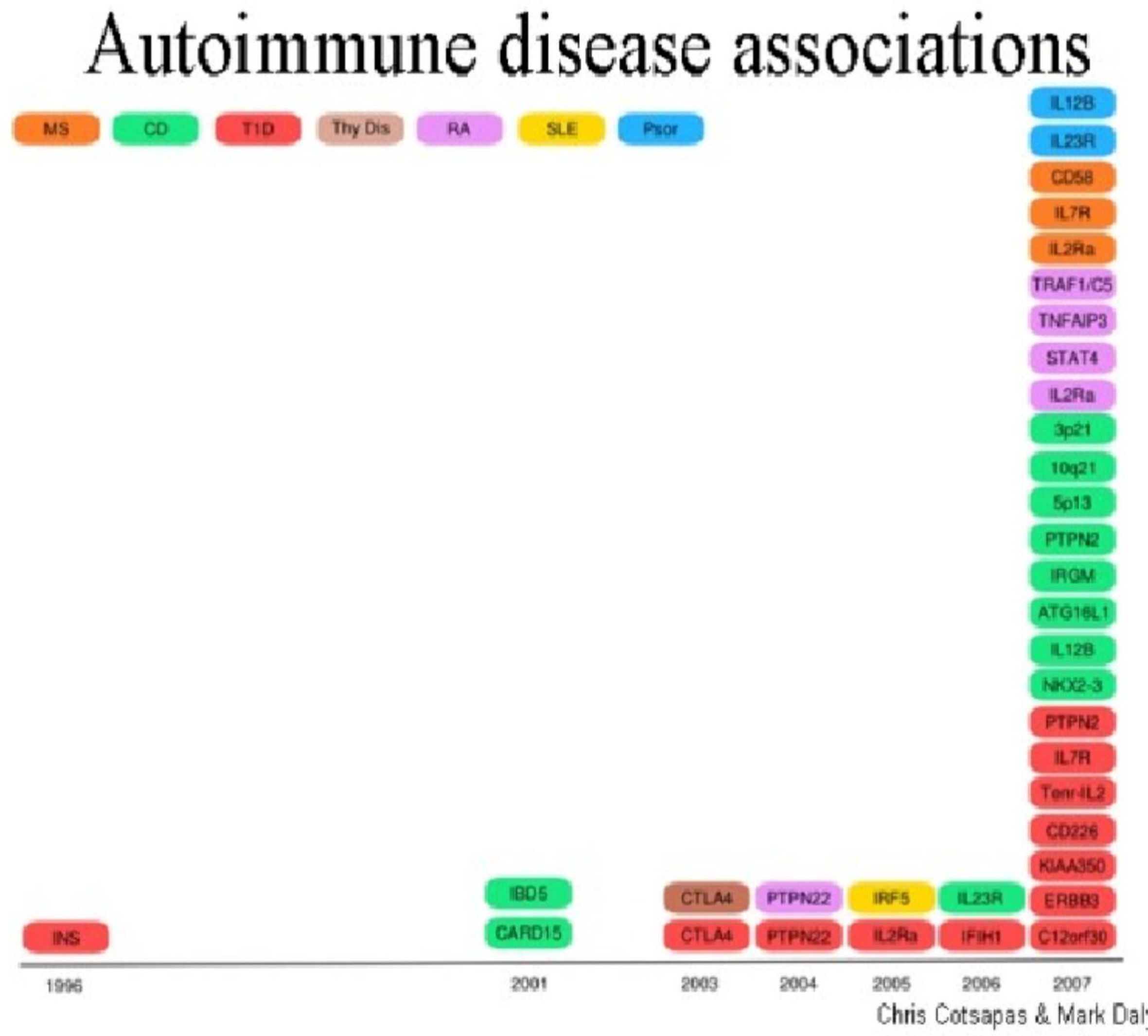
Vol 447 | 7 June 2007 | doi:10.1038/nature05911 nature

ARTICLES

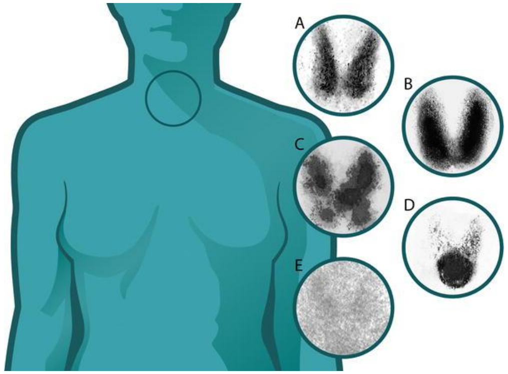
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

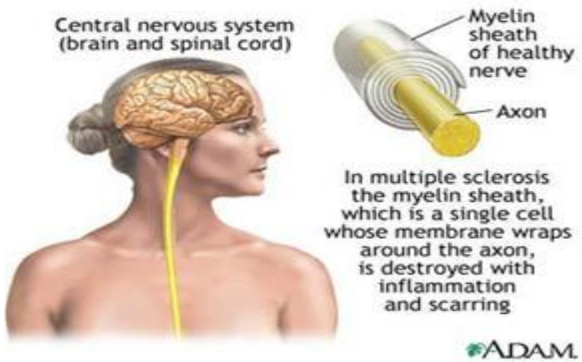
The Wellcome Trust Case Control Consortium*

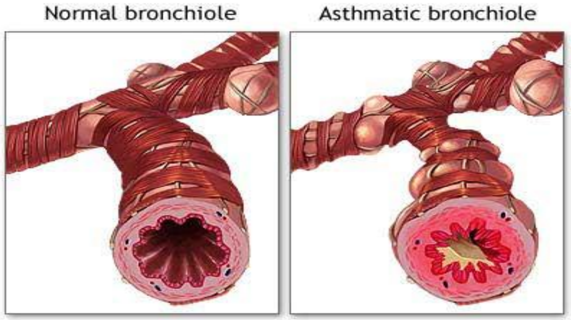
There is increasing evidence that genome-wide association (GWA) studies represent a powerful approach to the identification of genes involved in common ...



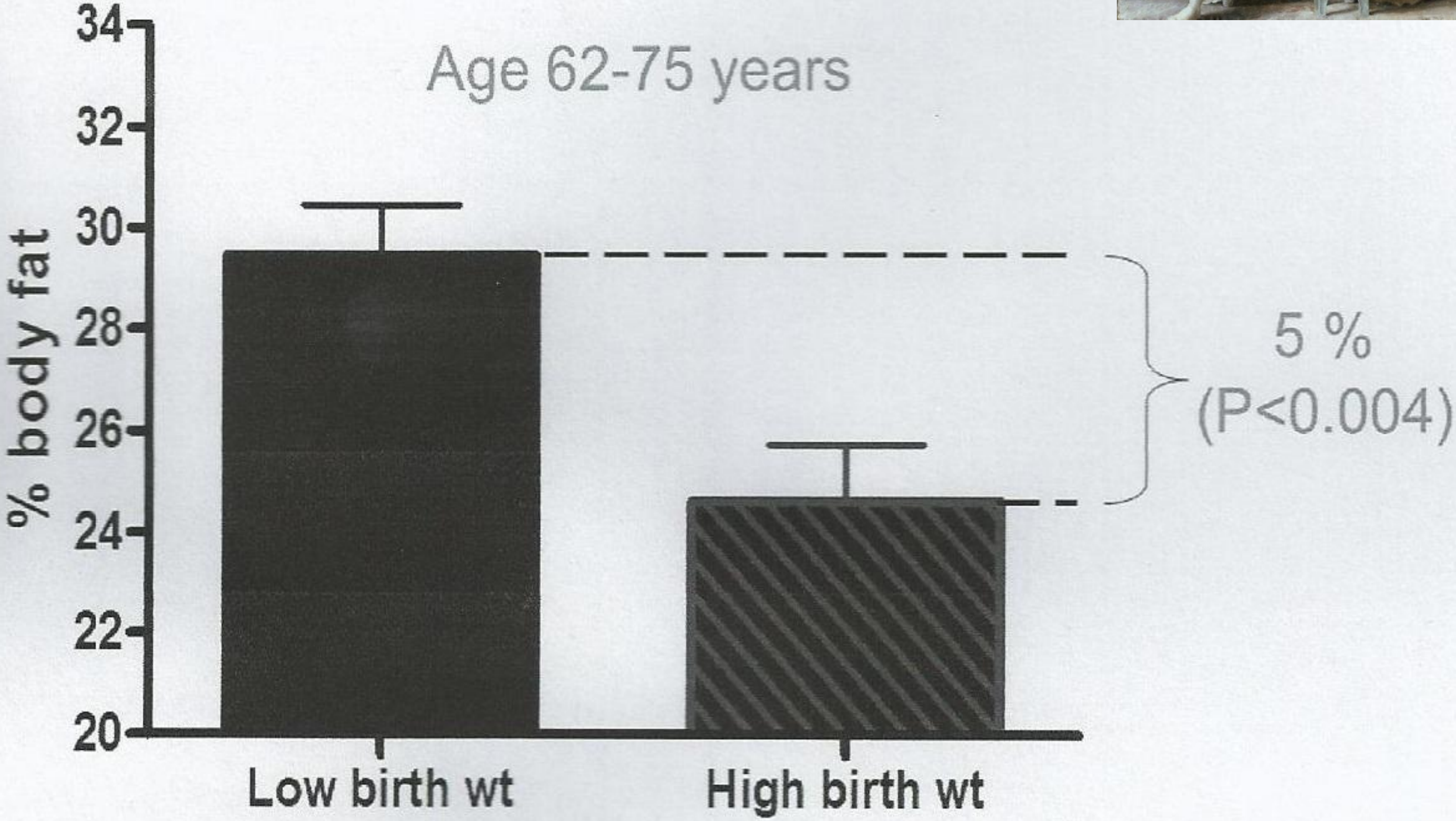
COMMON VARIANTS - MULTIPLE DISEASE & DIABETES







The birth weight focus



Kensara et al, 2005

adjusted for BMI

Glucose (a)

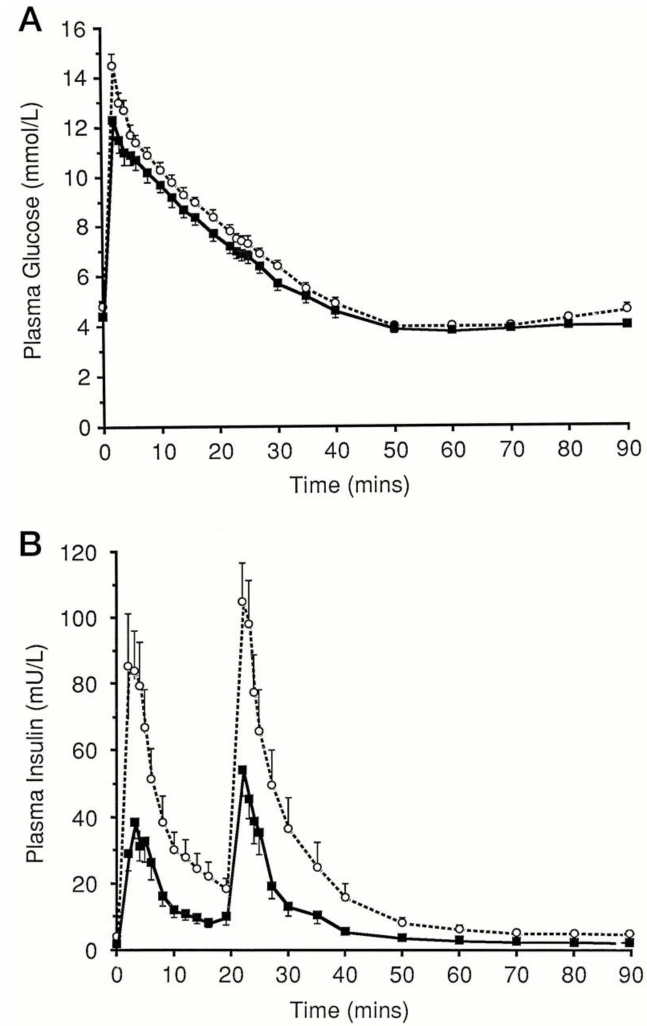
insulin (b)

profiles

normal
(closed boxes)

IUGR
(open circles)

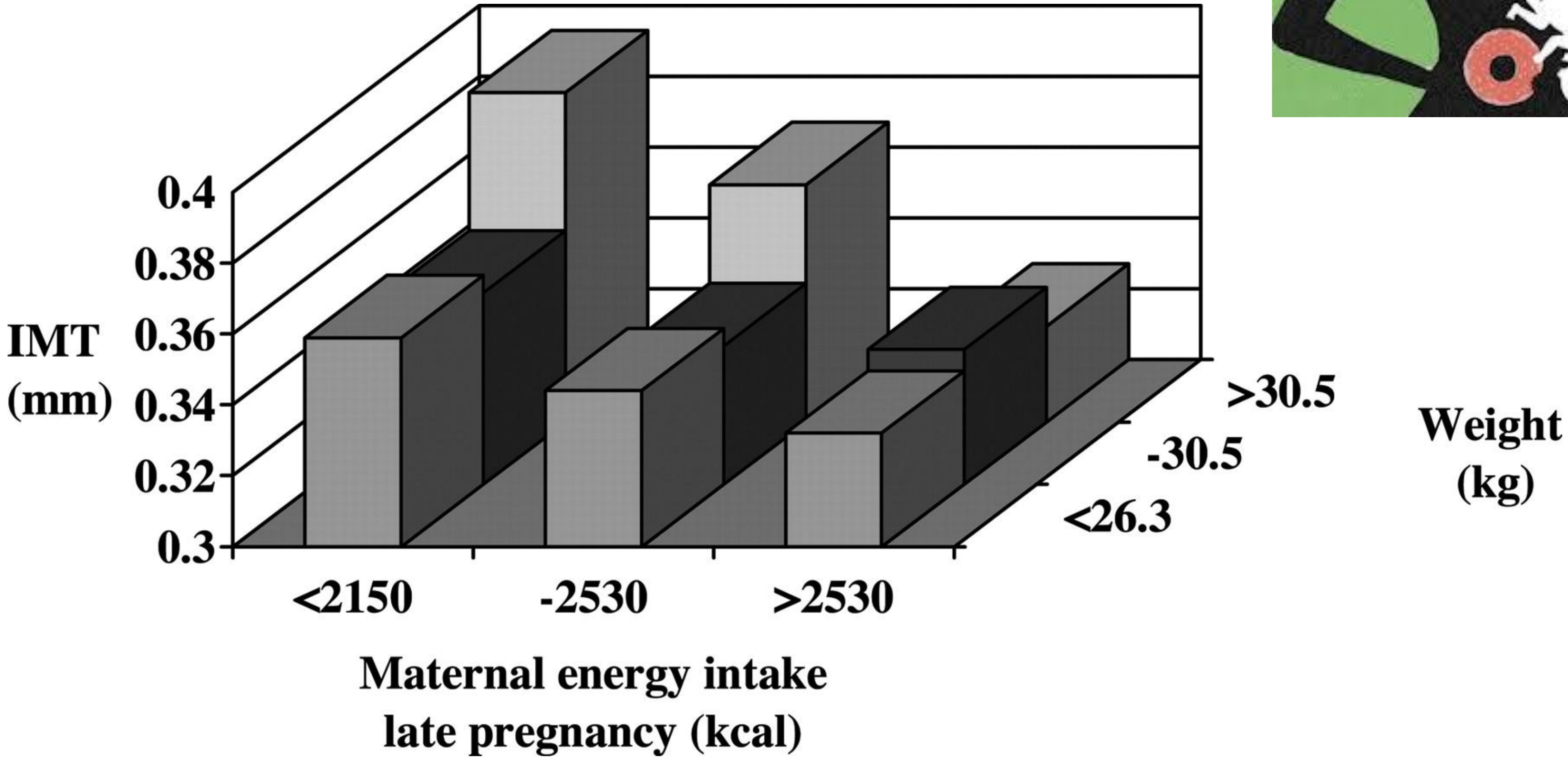
children,



Hofman P L et al. JCEM 1997;82:402-406

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Mean carotid IMT,
according to thirds of the distribution of current weight and maternal energy intake in late pregnancy.



Gale C R et al. Arterioscler Thromb Vasc Biol 2006;26:1877-1882

American Heart Association

Learn and Live

Undernutrition: Dutch Hunger

- In winter 1944-45, western region of Netherlands
  - limited food rations 400-800 cal/day for a specific time period
  - ‘natural’ experiment of restriction during pregnancy, furthermore allowing to investigate the impact of the timing of restriction and identify the ‘critical periods’

Early gestation

- **No effect** on birth weight
- Higher risk of obesity
- Glucose intolerance
- Coronary heart diseases
- Adverse lipid profile and coagulation factors

mid-gestation

- Impact on renal function
- Glucose intolerance
- Lower insulin secretion indices

Late-gestation

- Lower birth weight,
- **Not** higher risk of obesity
- Glucose intolerance (independent of effect of lower birth weight)

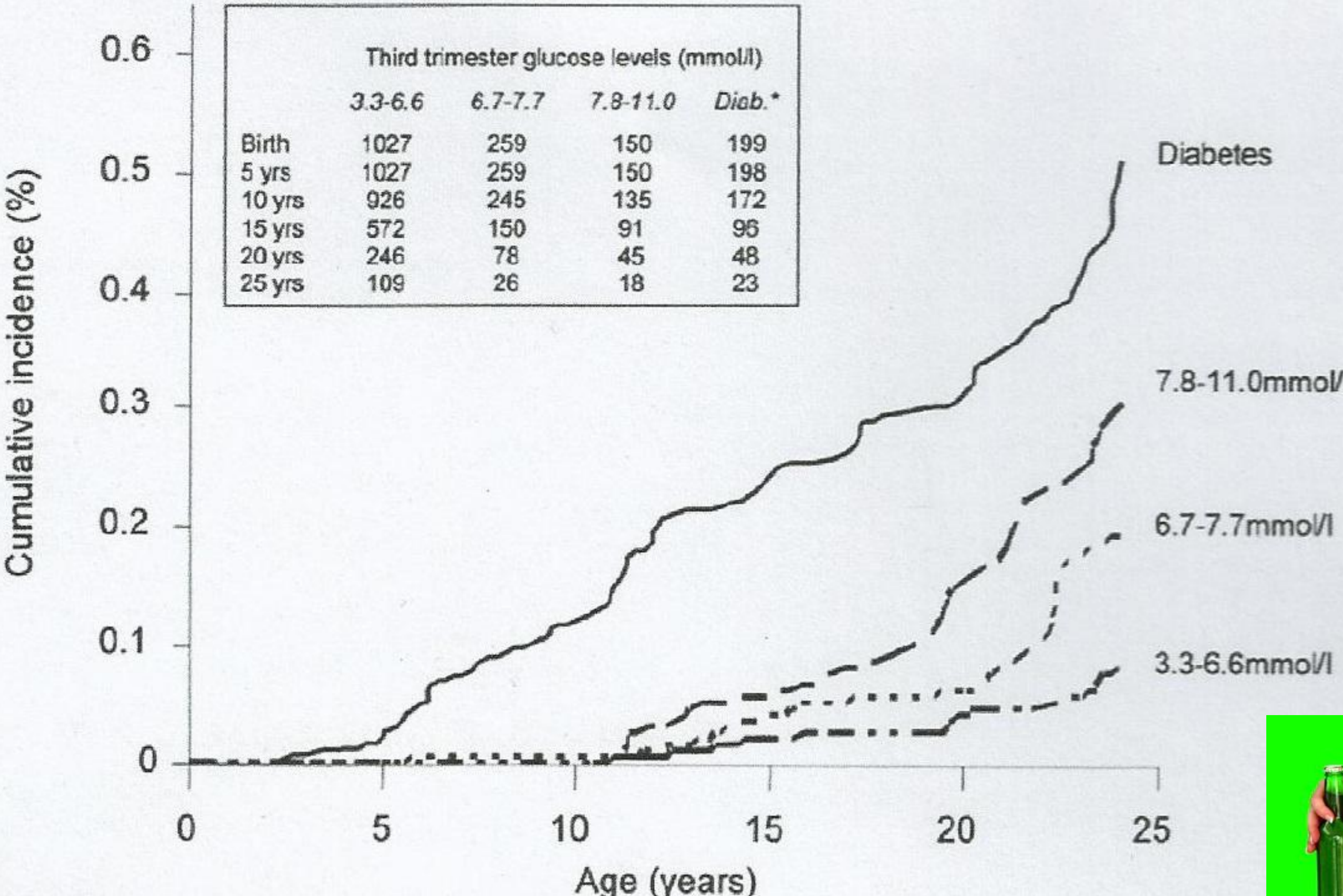
Roseboom T et al. Early Human Development 2006
Lumey LH et al. Int J Epidemiol 2007

Table 1.

Effects of Birth Weight on Hazard Ratios for Coronary Heart Disease and the Cumulative Incidence of Hypertension in Adult Men and Women

	Adult men		Adult women	
Birth weight (g)	***Hazard ratios for coronary heart disease***[a]	***Cumulative incidence of hypertension (%)***[b]	***Hazard ratios for coronary heart disease***[c]	***Cumulative incidence of hypertension (%)***[d]
≤ 2500	3.63	—	1.34	—
2501–3000	1.86	19.0	1.38	21.1
3001–3500	1.99	17.0	1.24	16.3
3501–4000	2.08	14.1	1.17	13.0
> 4000	1.00	12.5	1.00	12.1

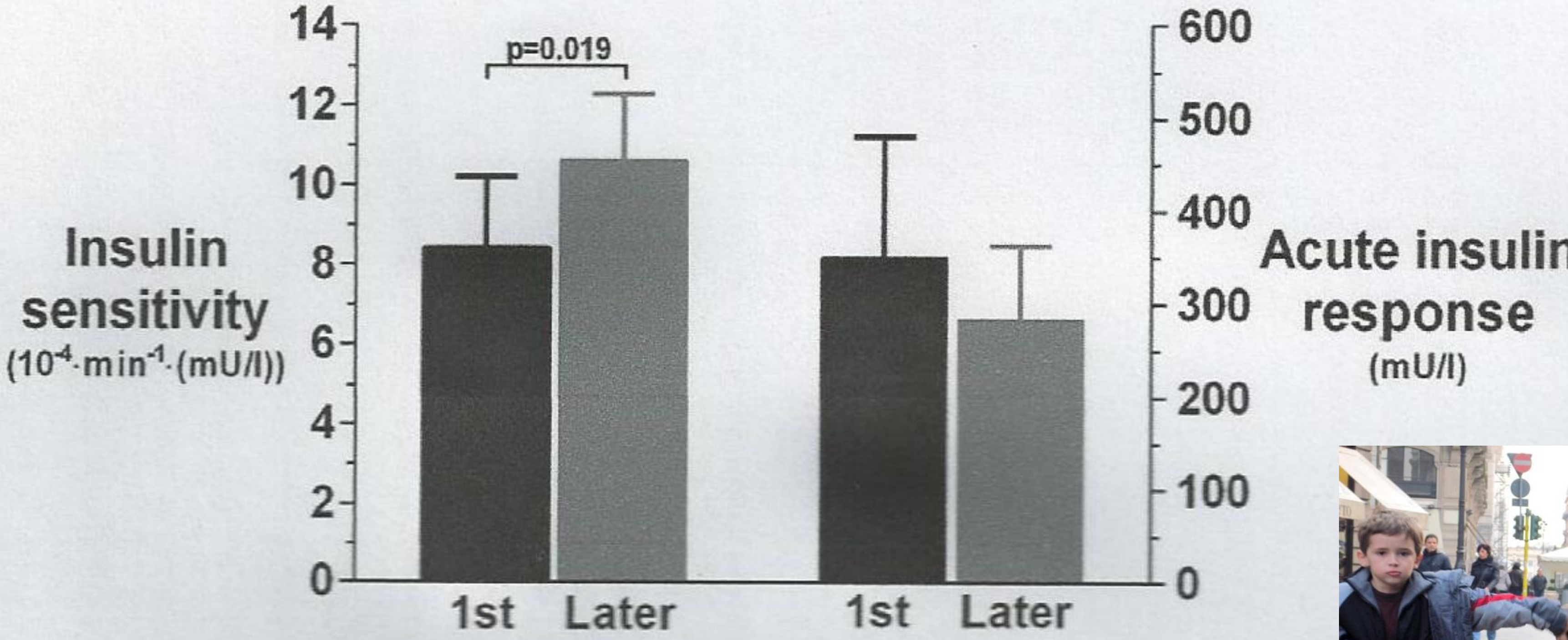
Cumulative incidence of T2D in Pimas offspring according to maternal 2h-glucose at third trimester



	Third trimester glucose levels (mmol/l)			
	3.3-6.6	*6.7-7.7*	*7.8-11.0*	*Diab.**
Birth	1027	259	150	199
5 yrs	1027	259	150	198
10 yrs	926	245	135	172
15 yrs	572	150	91	96
20 yrs	246	78	45	48
25 yrs	109	26	18	23

Franks PW et al. Diabetes 2006

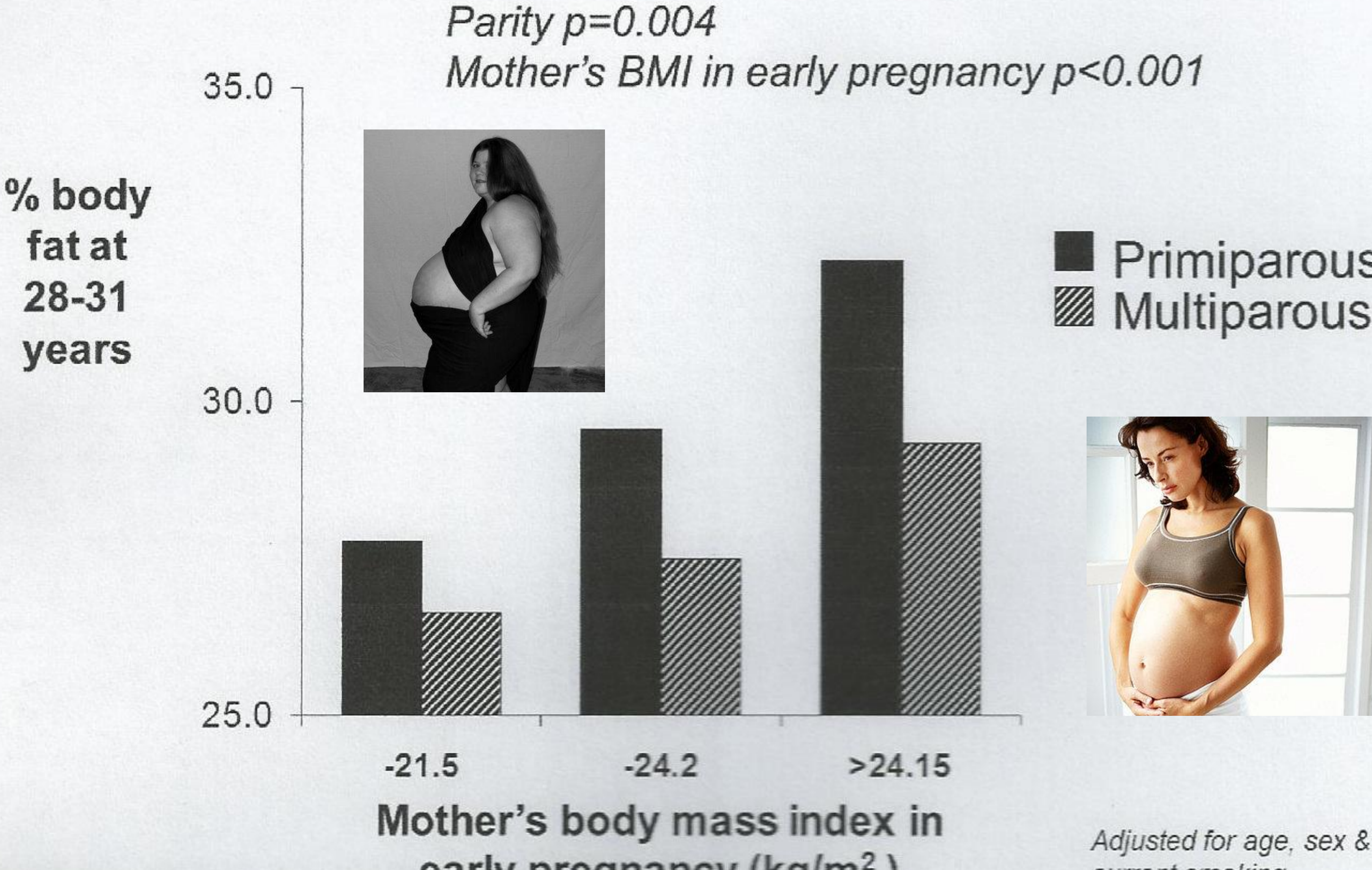
Insulin sensitivity and acute insulin response among first-born and later-born children.



n = 85 (32 1st born, 53 later born)

Ayyavoo A et al. JCEM 2013;98:1248-1253

The impact of parity



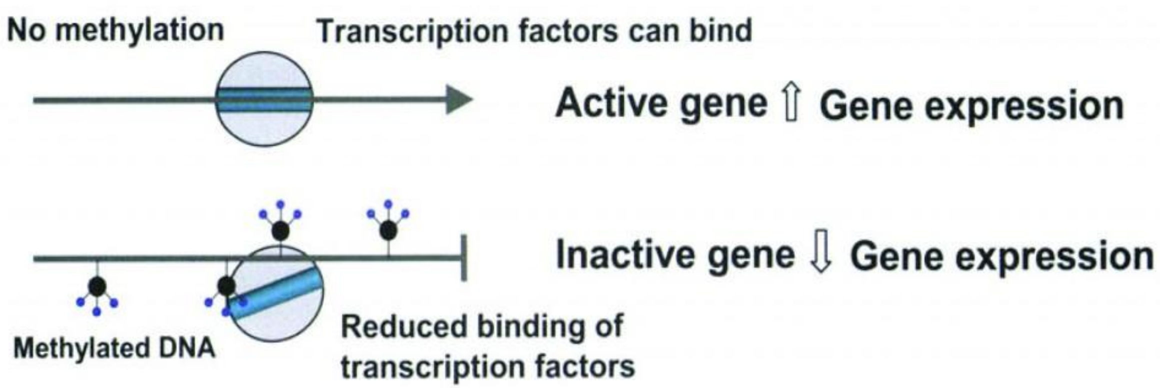
Adjusted for age, sex & current smoking

Godfrey et al – JCEM 2010

ENVIRONMENTAL EFFECTS

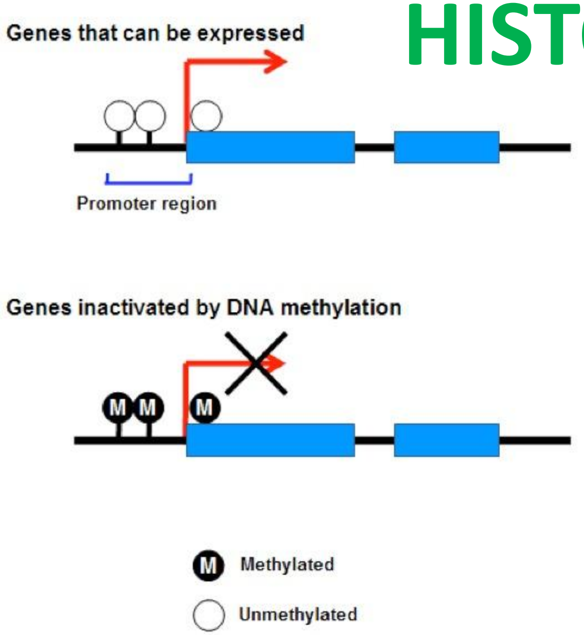
- **DISRUPTIVE (teratogenesis) mutations**

- **ADJUST (developmental plasticity) epigenetics**



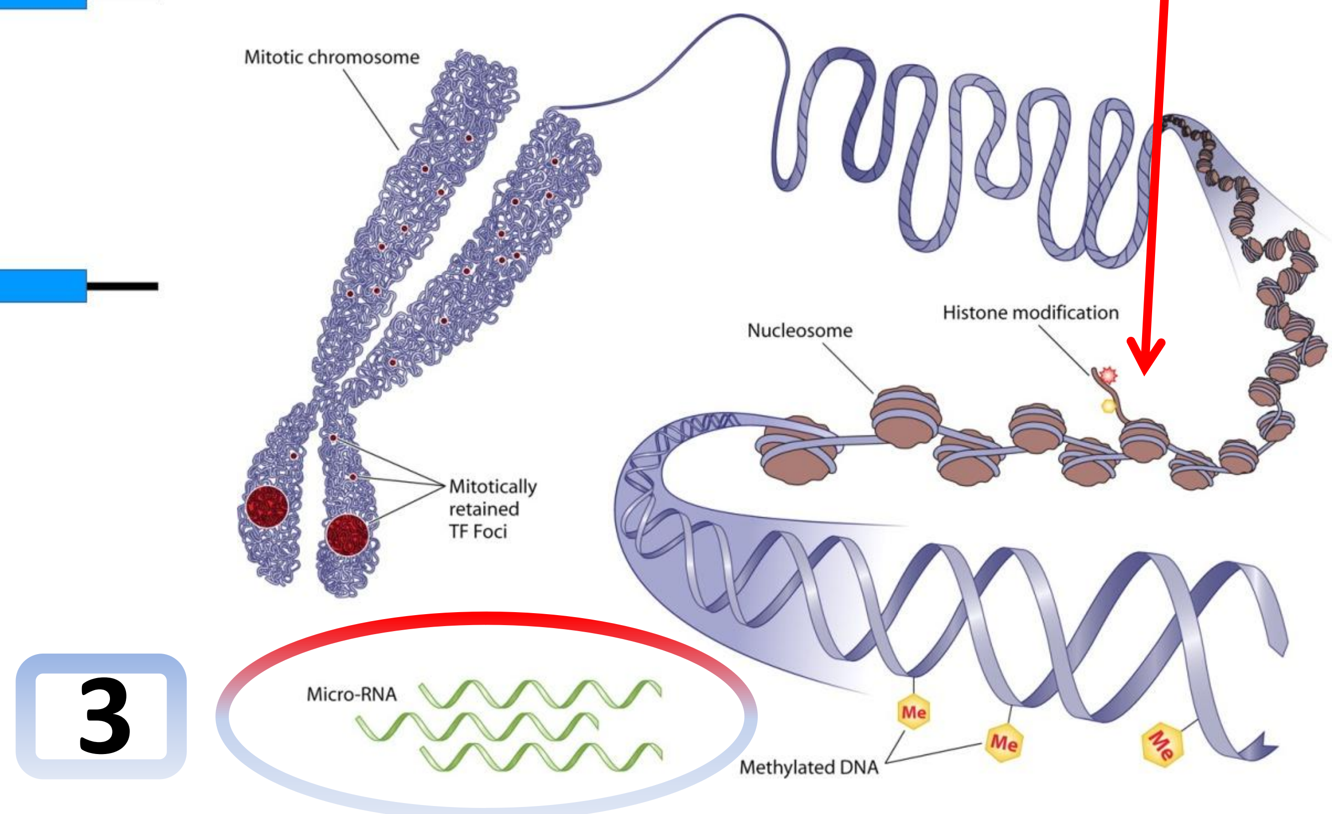
METHYLATION
PROMOTER ACTIVITY
micro RNA
HISTONE ACETYLATION

1

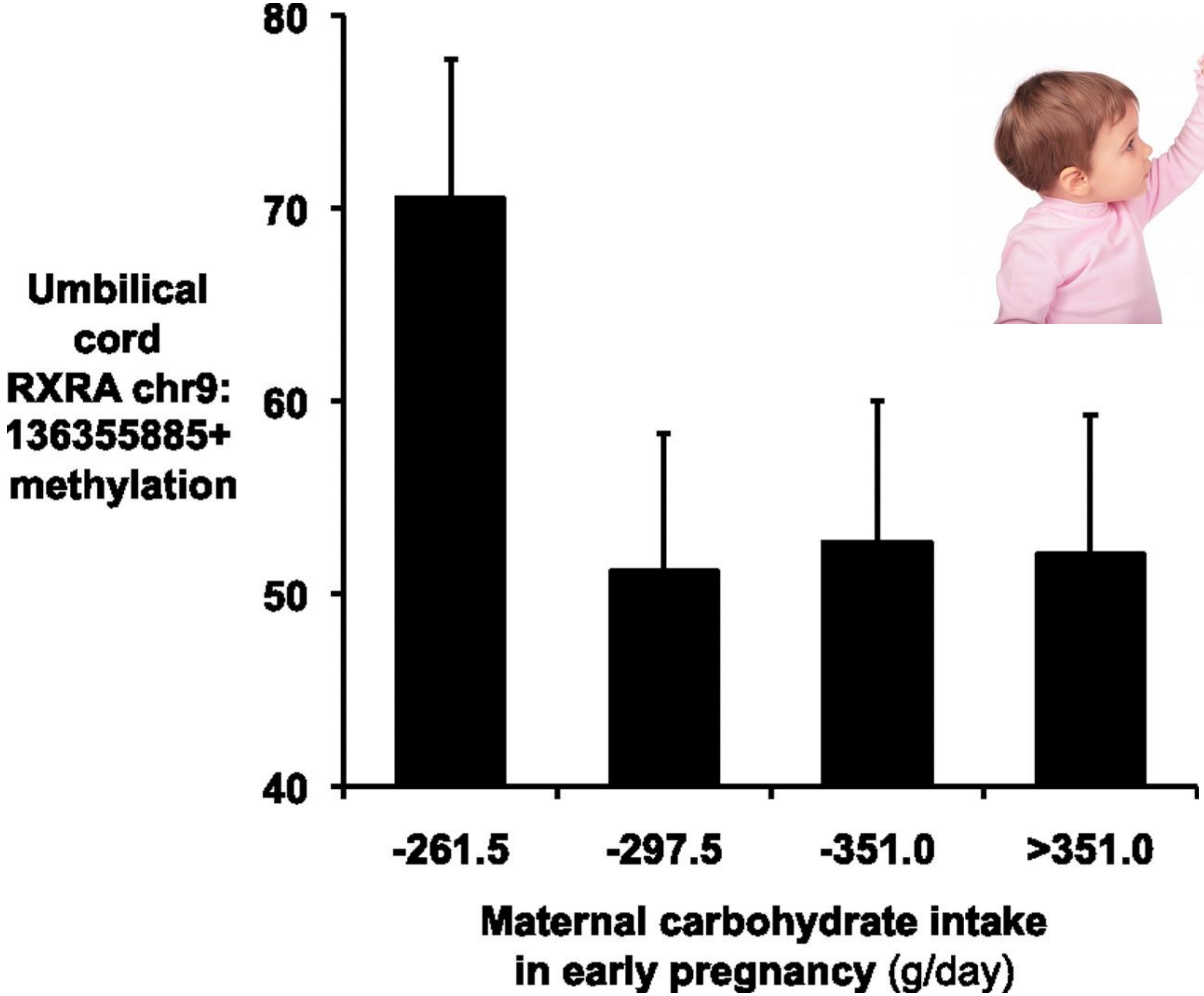


2

DNA repair

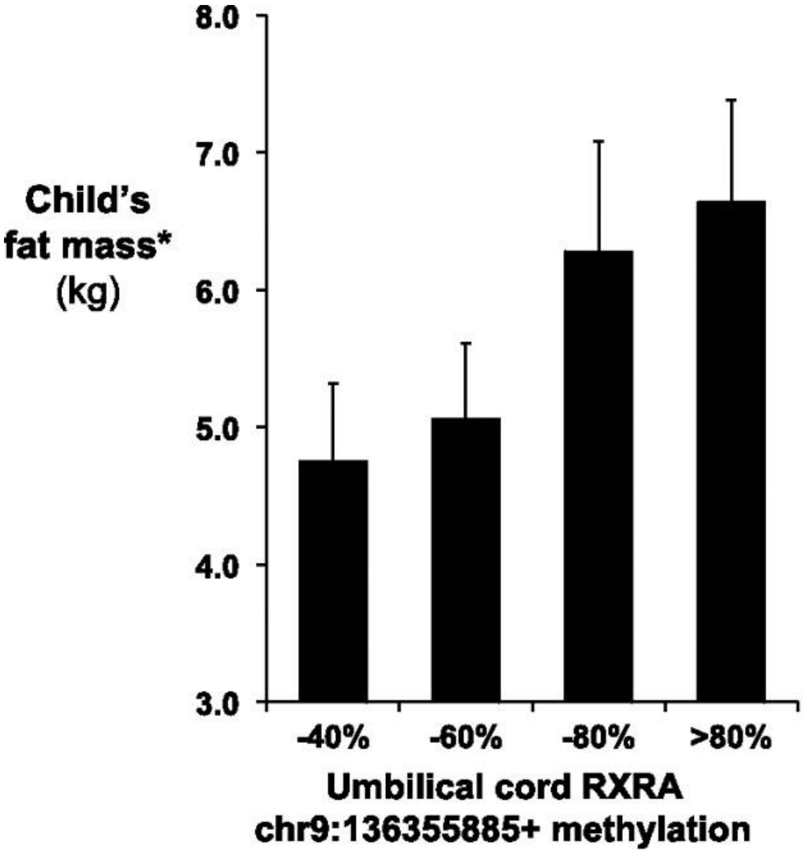


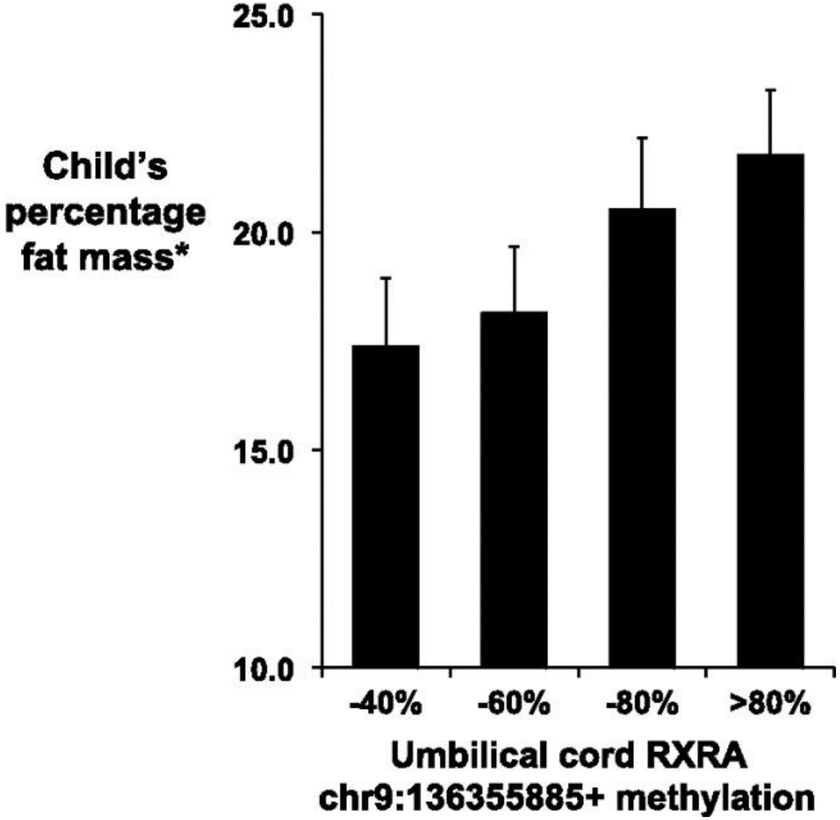
Lower maternal carbohydrate in early pregnancy is associated with higher umbilical cord RXRA chr9:136355885+ methylation in the PAH cohort.



Godfrey K M et al. Diabetes 2011;60:1528-1534

Child's %fat mass & fat mass at age 9 years increase with higher umbilical cord RXRA chr9:136355885+ methylation





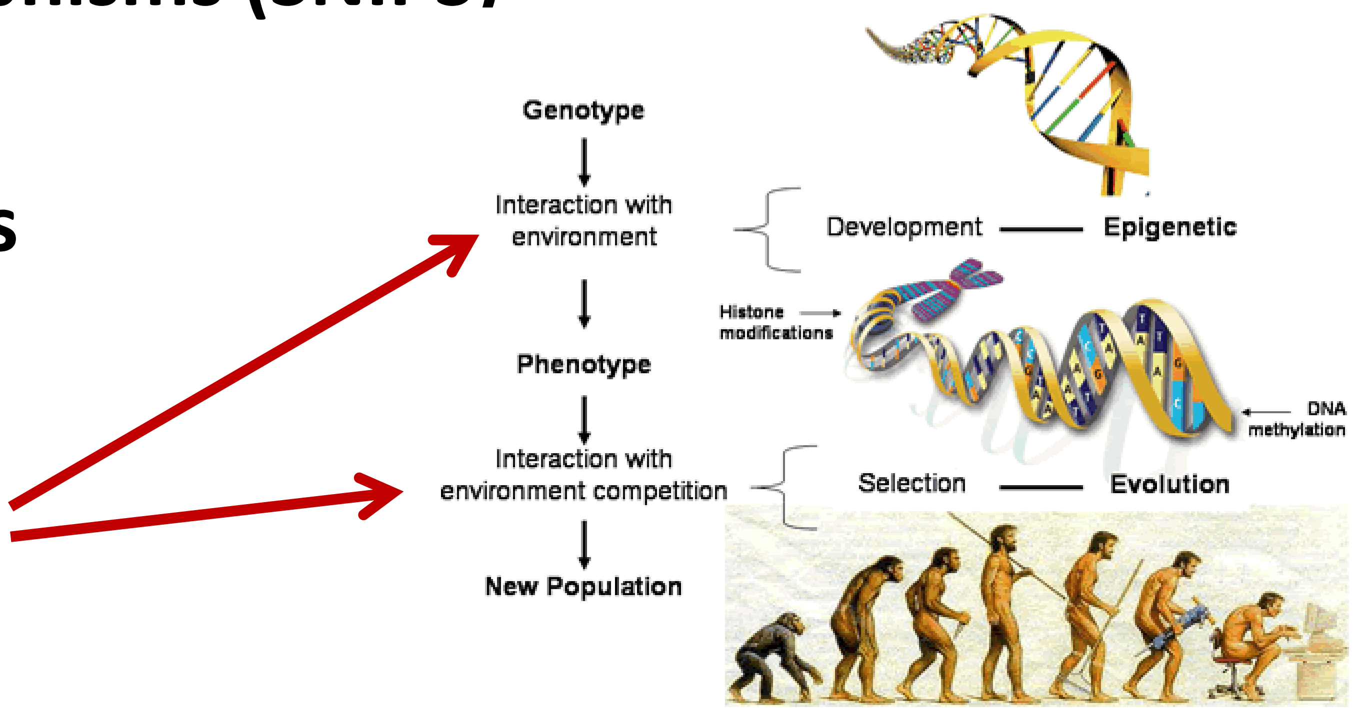
Godfrey K M et al. Diabetes 2011;60:1528-1534

American Diabetes Association.

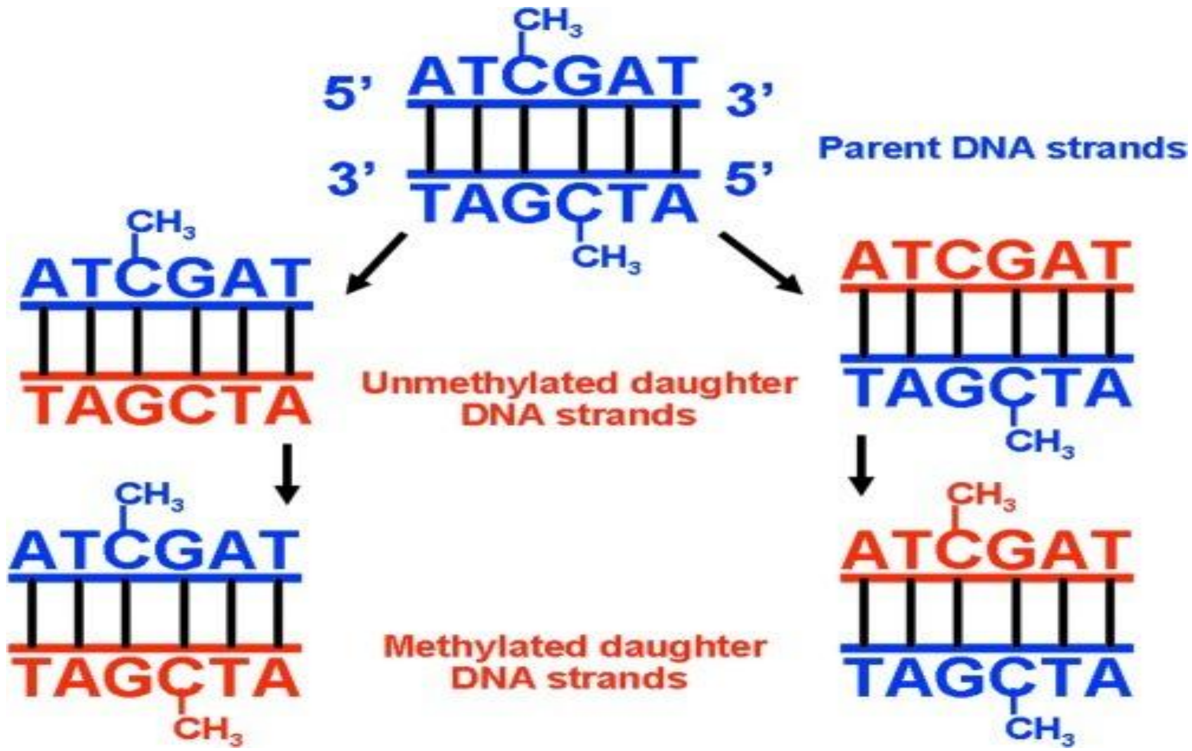
ENVIROMENT & EVOLUTION

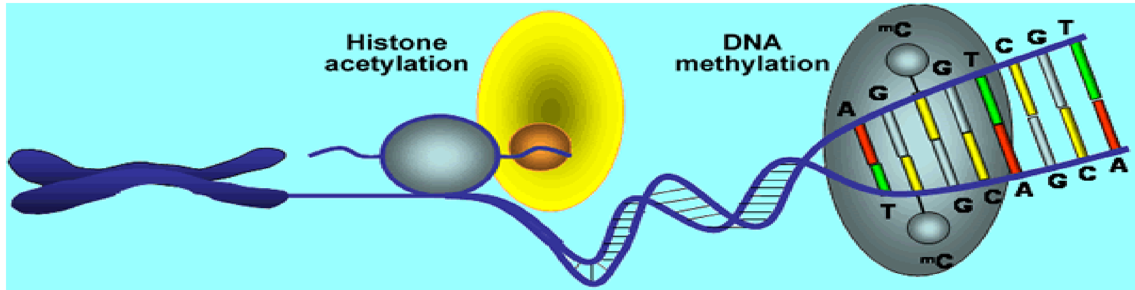
- **Parental inheritage**
- **Polymorphisms (SNIPS)**
- **Cell types**

EPIGENOMICS



PARENTAL EPIGENOMICS

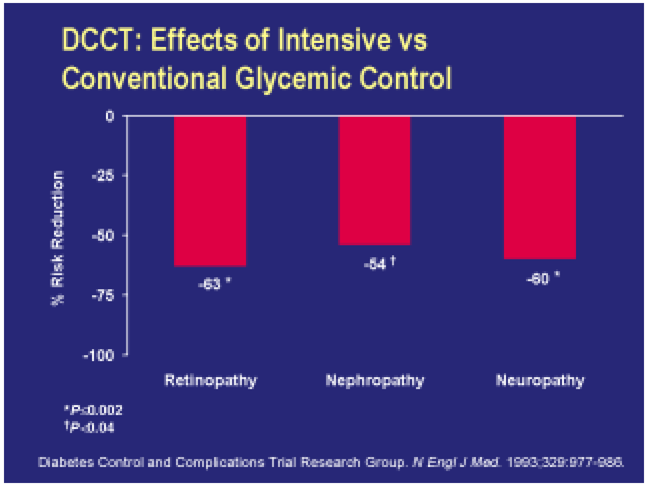




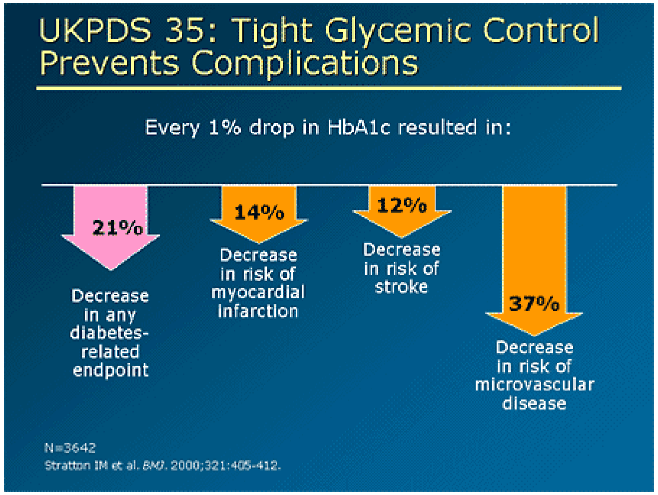
CHRONIC DIABETES COMPLICATIONS

- **Diabetic complications progress in spite of glucose control**

DCCT



UKPDS

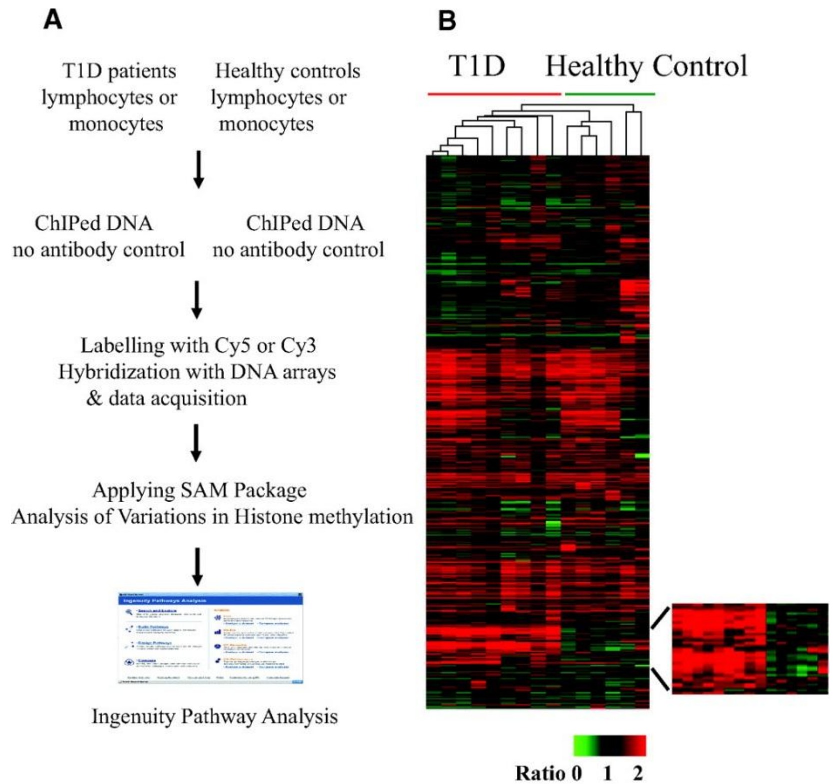


OBJECTIVES

- Changes in covalent histone modifications in chromatin (epigenetic mechanisms) regulating the transcription of Inflammatory Genes (TNFα IL-6, MCP-1) and Fibrotic Genes (*Collagen, CTGF, PAI-1*) under Diabetic conditions
- Functional Relevance of chromatin changes to increased inflammation and Metabolic Memory in Diabetes
- Genome-Wide Profiling of Modified Histones with ChIP-on-chips and ChIP-Seq (Epigenomics)

Epigenetics: Heritable changes in gene expression that occur without a change in DNA sequence.
The Structural Adaptation of chromosomal regions so as to register, Signal or perpetuate altered Activity States (*Bird, 2007*)

Profiling histone lysine methylation in blood cells from type 1 diabetic (T1D) patients vs healthy control subjects.



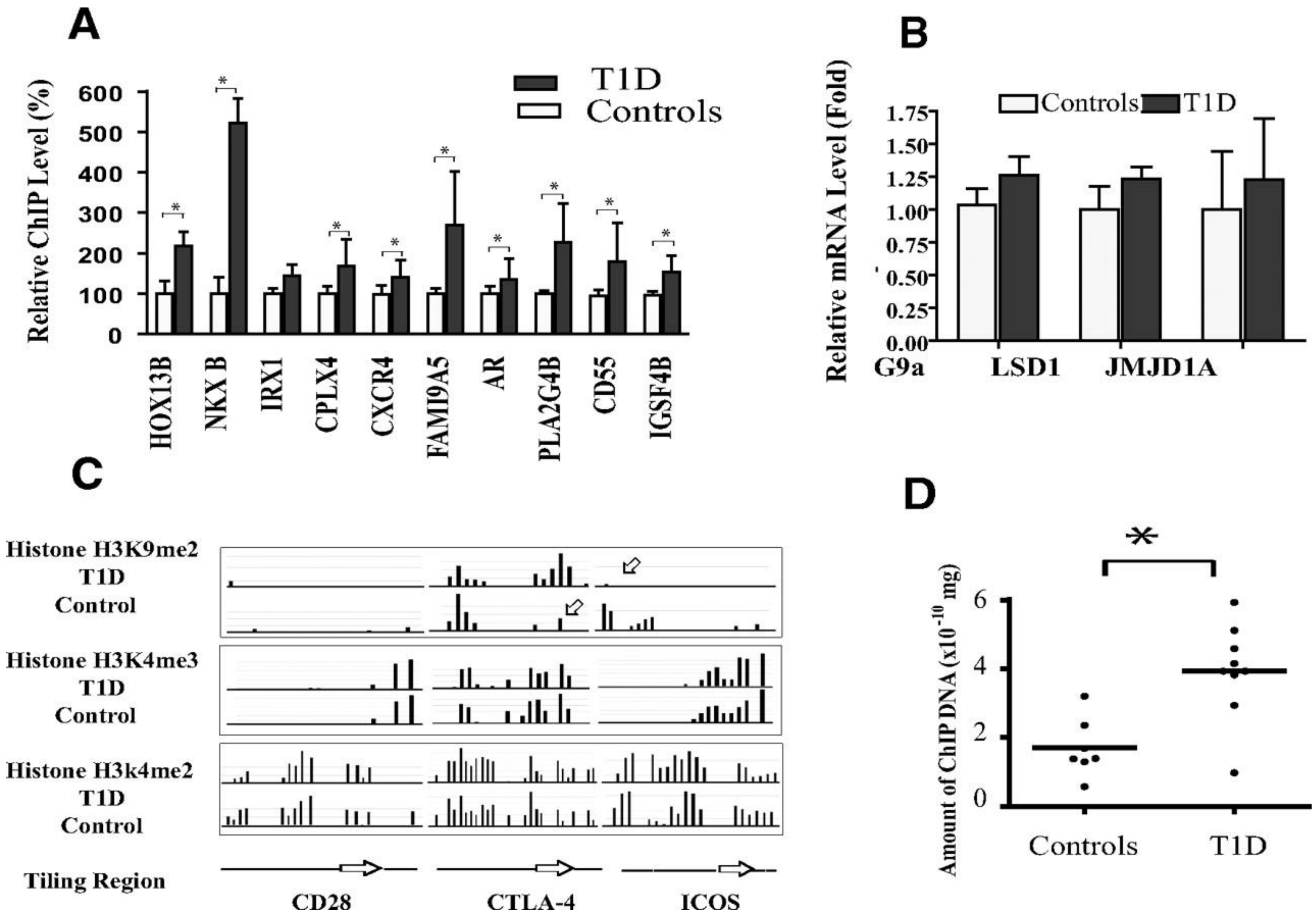
C

Demographics	Normal (N=7)	Diabetes (N=9)	p-value
Median Age Years (Range)	43 (35 – 60)	60 (25 – 85)	0.25
Gender Male/Female %	29% / 71%	33% / 67%	0.84
Median Hemoglobin A1c % (Range)	--	7.5% (5.4% - 10.5%)	

Miao F et al. Diabetes 2008;57:3189-3198

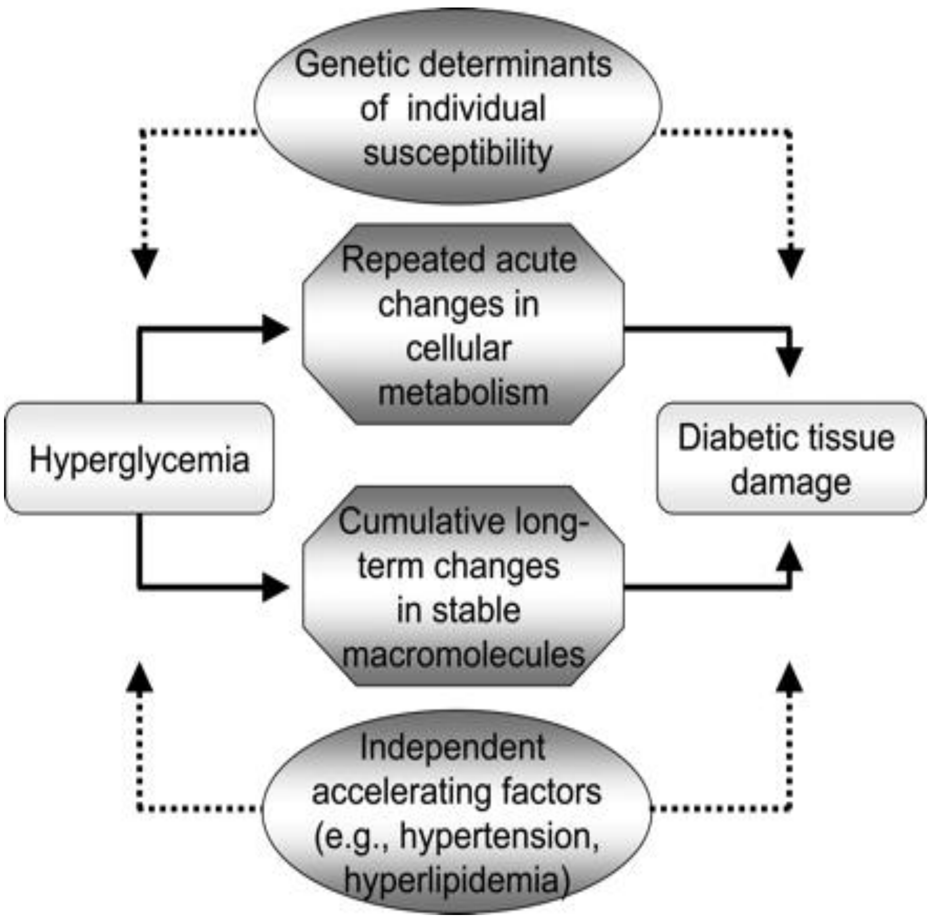
American Diabetes Association.

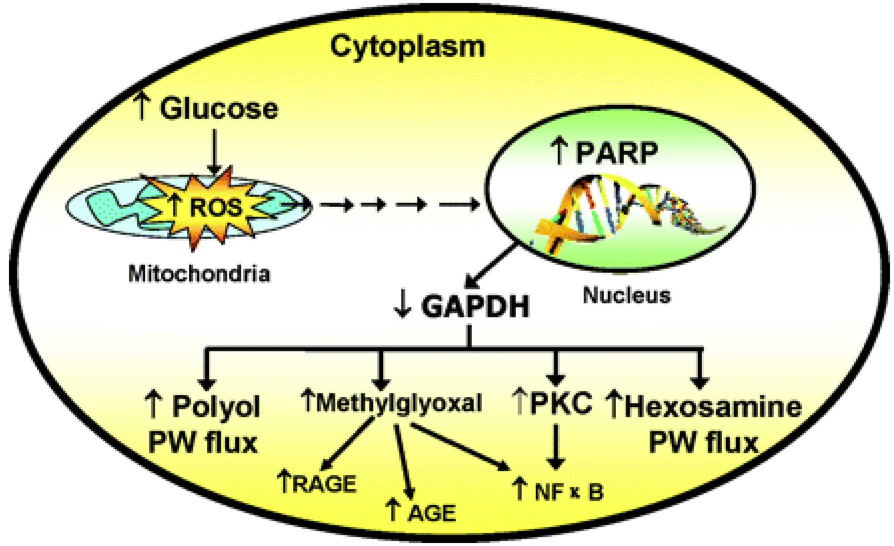
Validation of histone methylation alterations and quantification of histone methylase/demethylase mRNA levels in type 1 diabetic patients and healthy control subjects.

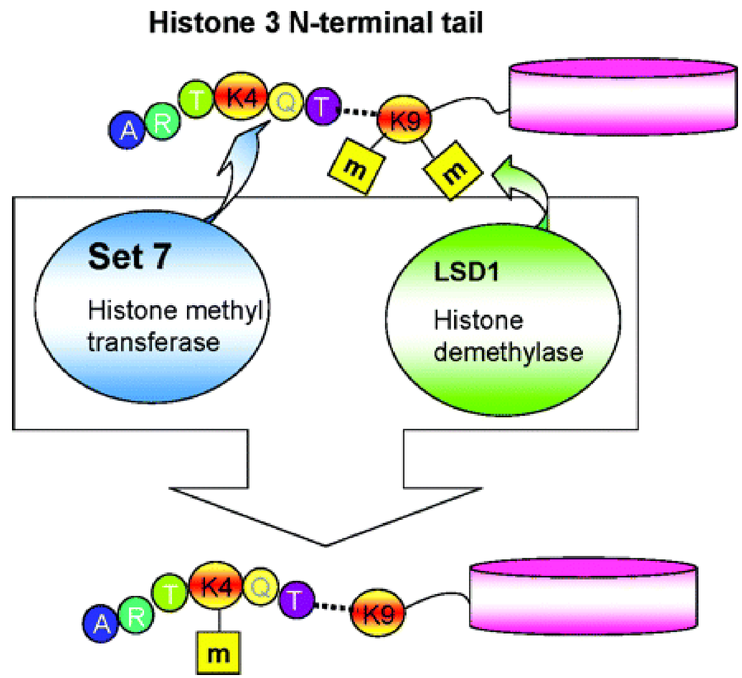


Miao F et al. Diabetes 2008;57:3189-3198

Oxidative Stress and Diabetic Complications



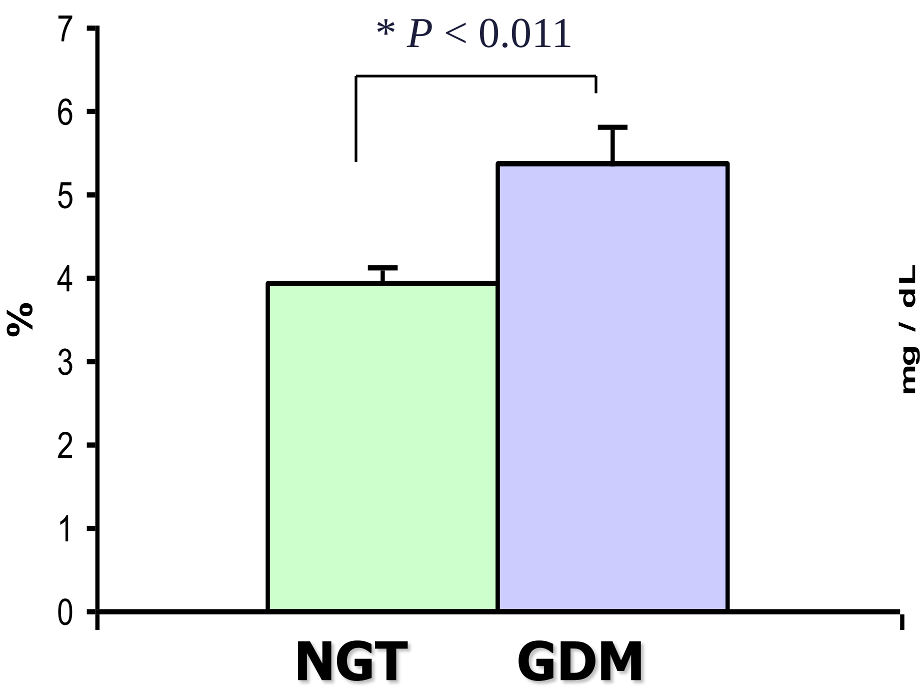




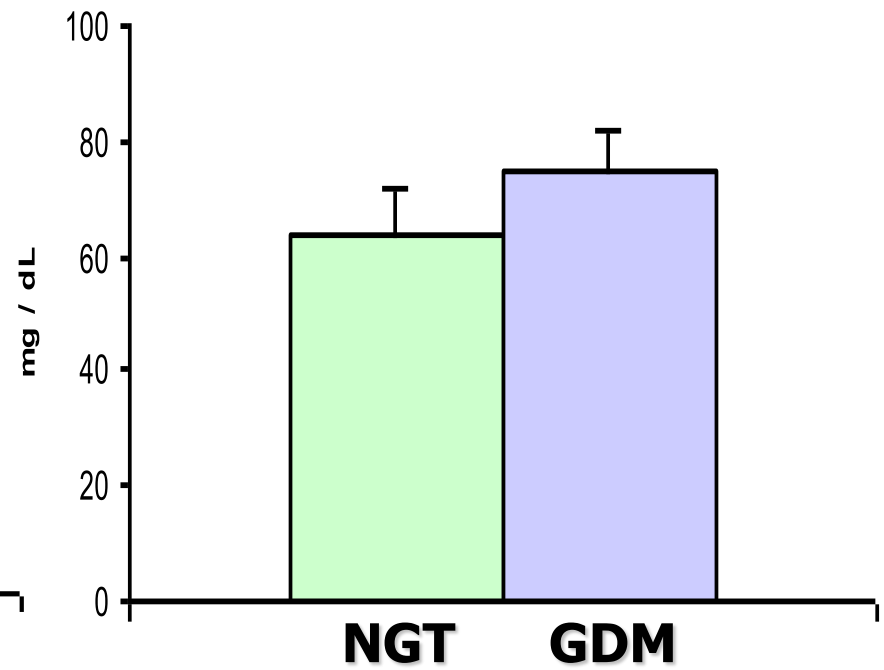
Circulation Research October 29, 2010 vol. 107 no. 9 1058-1070

GESTATIONAL DIABETES

GHbA1c

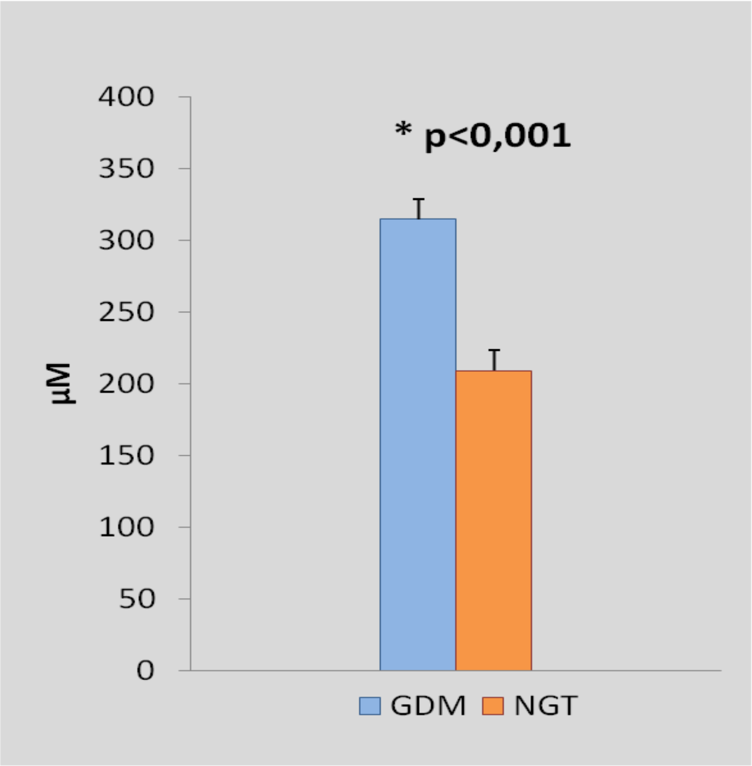


Fasting Blood Glucose

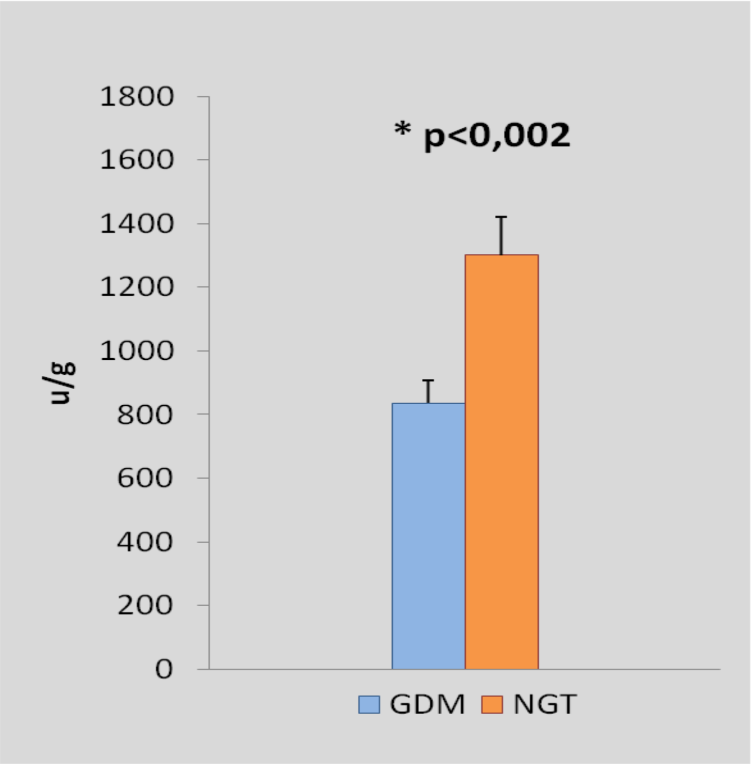


OXIDATIVE LOAD IN GESTATIONAL DIABETES

plasma hydrogen superoxide

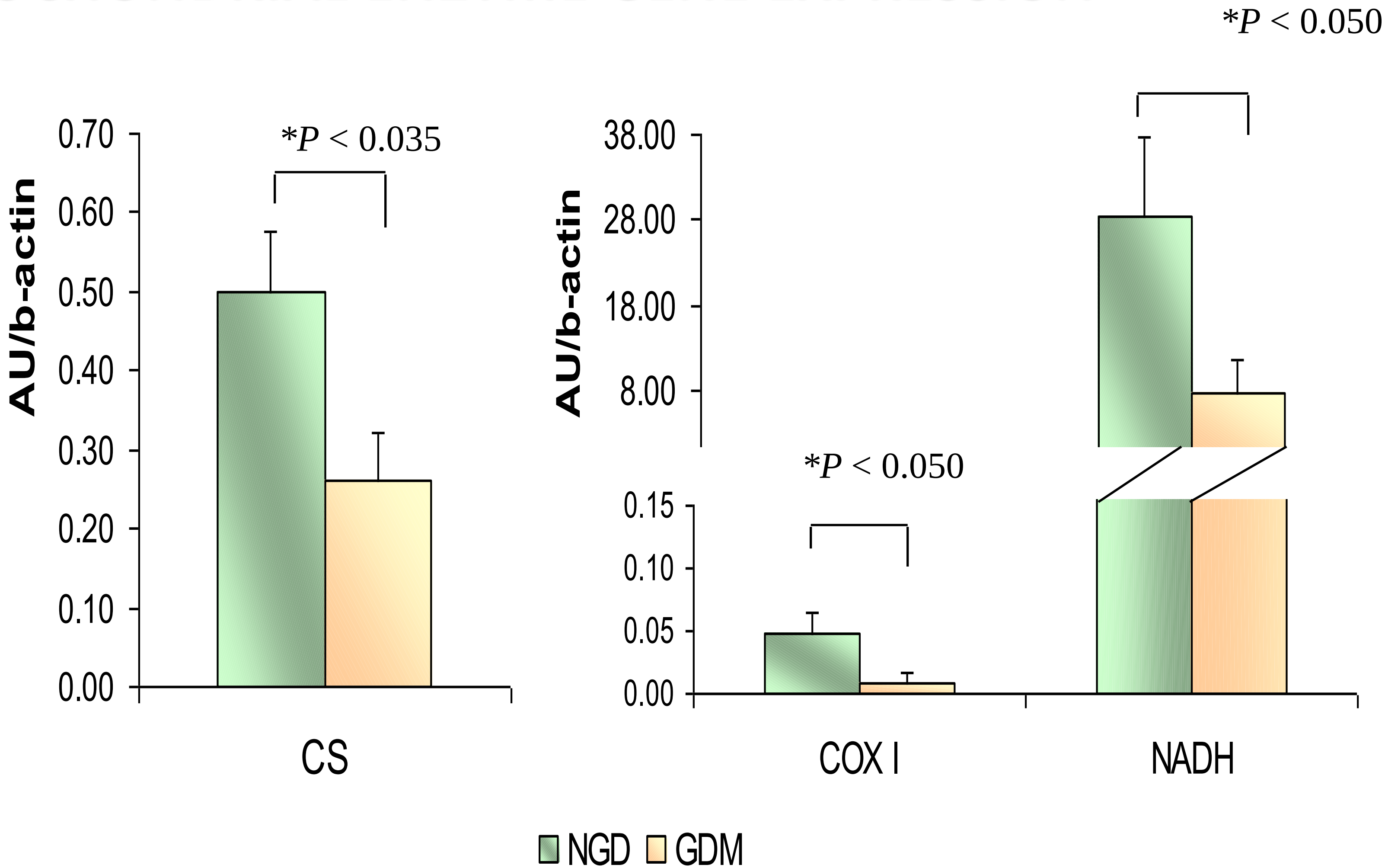


skeletal muscle SOD activity

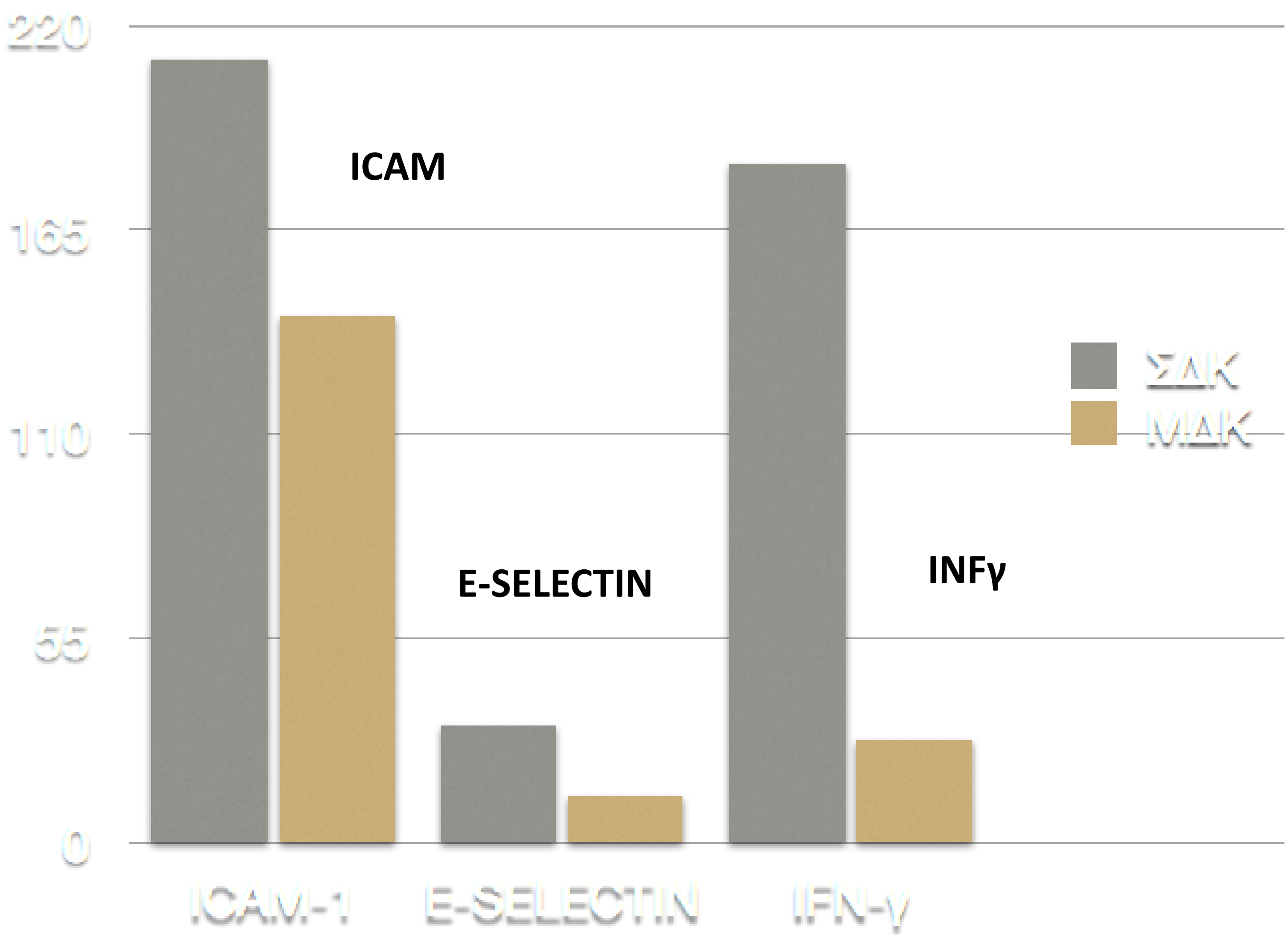


Halvatsiotis et al: American Diabetes Association Meeting 2010

Placental
MITOCHONDRIAL ENZYME GENE EXPRESSION

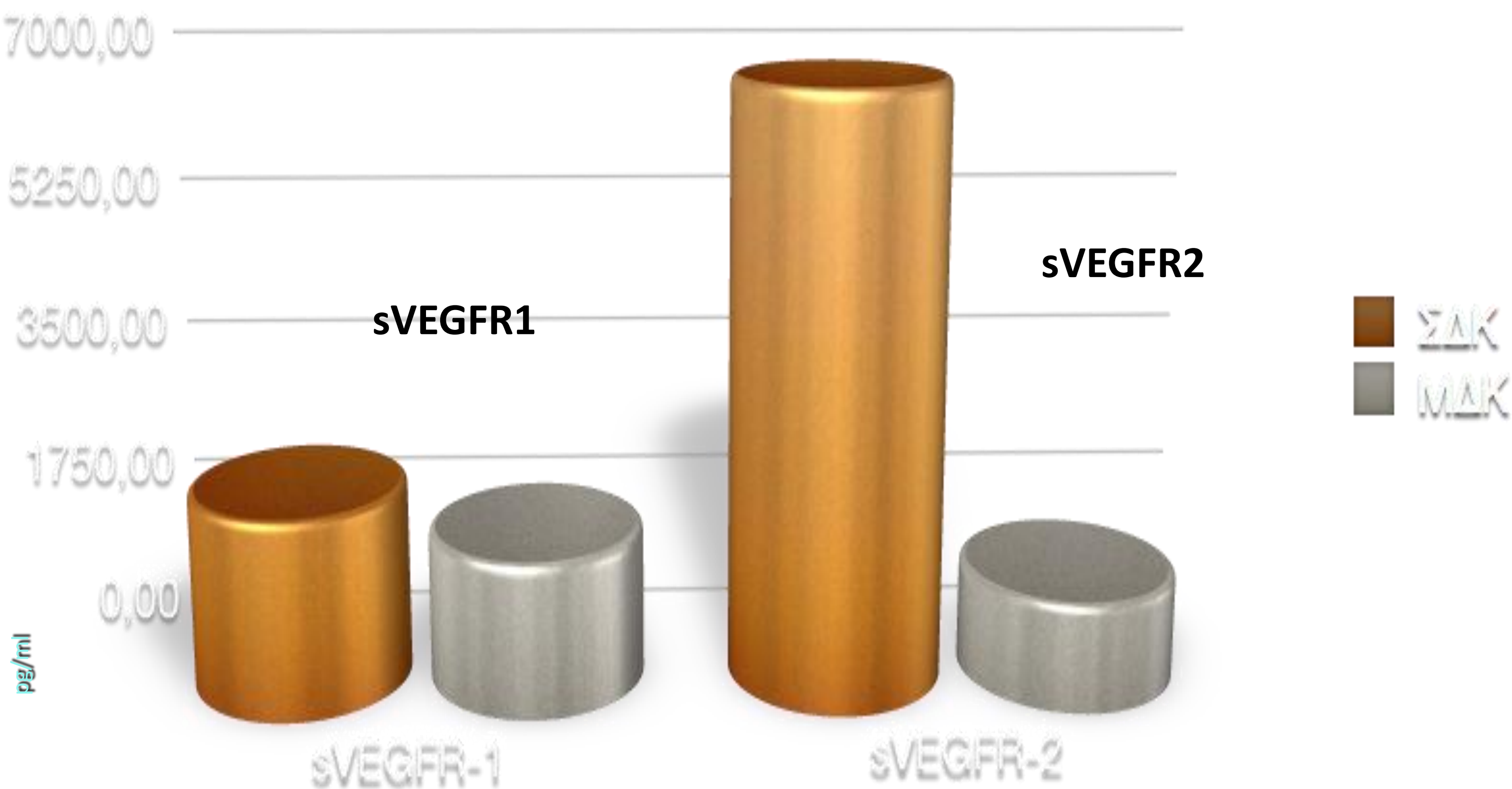


INFLAMMATORY MARKERS



sVASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTORS (pg/ml)

	NGT	GDM	P values
sVEGFR-1	1746.24 ± 36.8	2239.03 ± 170.5	0.004*
sVEGFR-2	1230.92 ± 234.2	6759.52 ± 1071.5	0.0004*

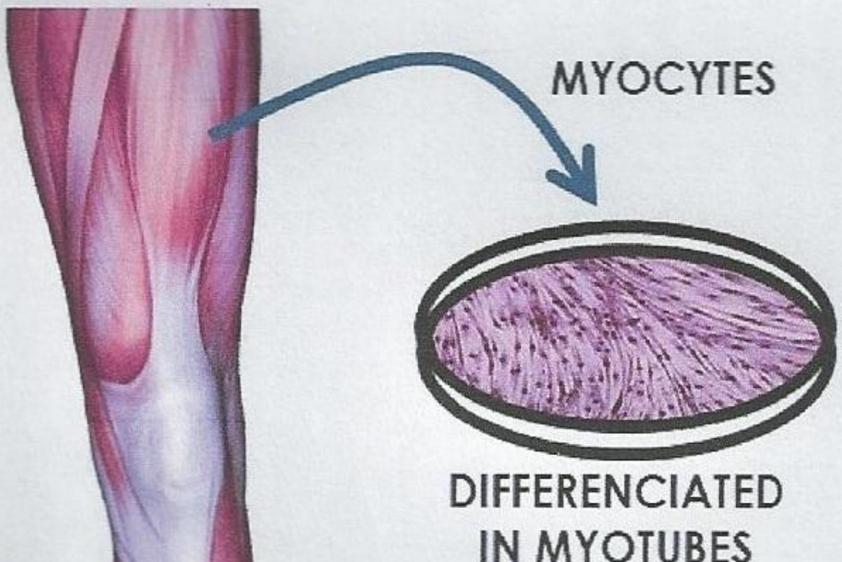


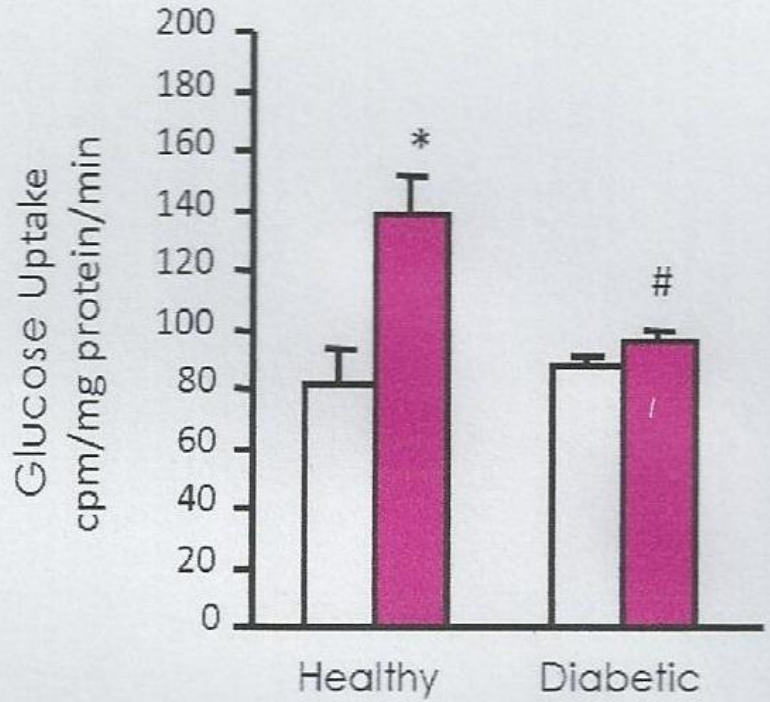
	Φ.Τ	ΣΔΚ
ATF2	7,17	52,16
GATA3	2,08	5,17
ILIORA	50	22,9
IL12A	49,01	26,49
IL12B	50	33,58
IL13	71,55	50
IL13RA1	75,8	50
IL17C	71,3	50
IL17RA	18,84	13,5
IL4R	50	14,42
IL6R	11,38	0,04
IL6ST	25,22	4,79
IL7	20,24	0,57
INHA	19,28	0,72
TYK2	40,25	18,61

	Φ.Τ	ΣΔΚ
CCL25	50	44,08
CXCL14	35,64	3,14
CXCL3	22,08	0,4
CXCL5	26,66	3,4
CXCL6	27,53	0,88
FADD	12,89	0,21

GESTASIONAL DIABETES EPIGENETICS

NON-GENETIC MEMORY OF DIABETIC PHENOTYPE IN PRIMARY HUMAN MUSCLE CELL CULTURES

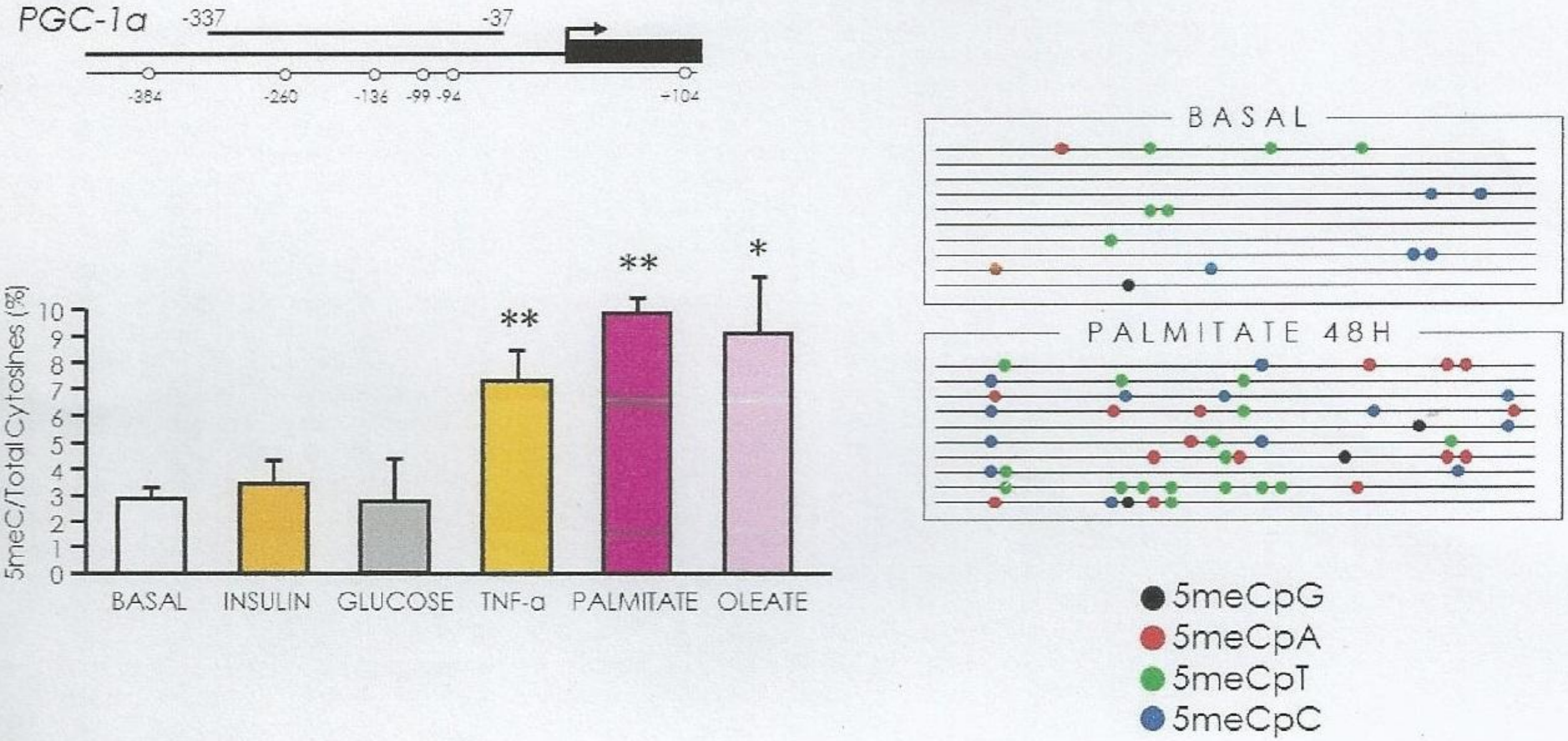




Bouzakri and Zierath, J. Biol. Chem, 2007

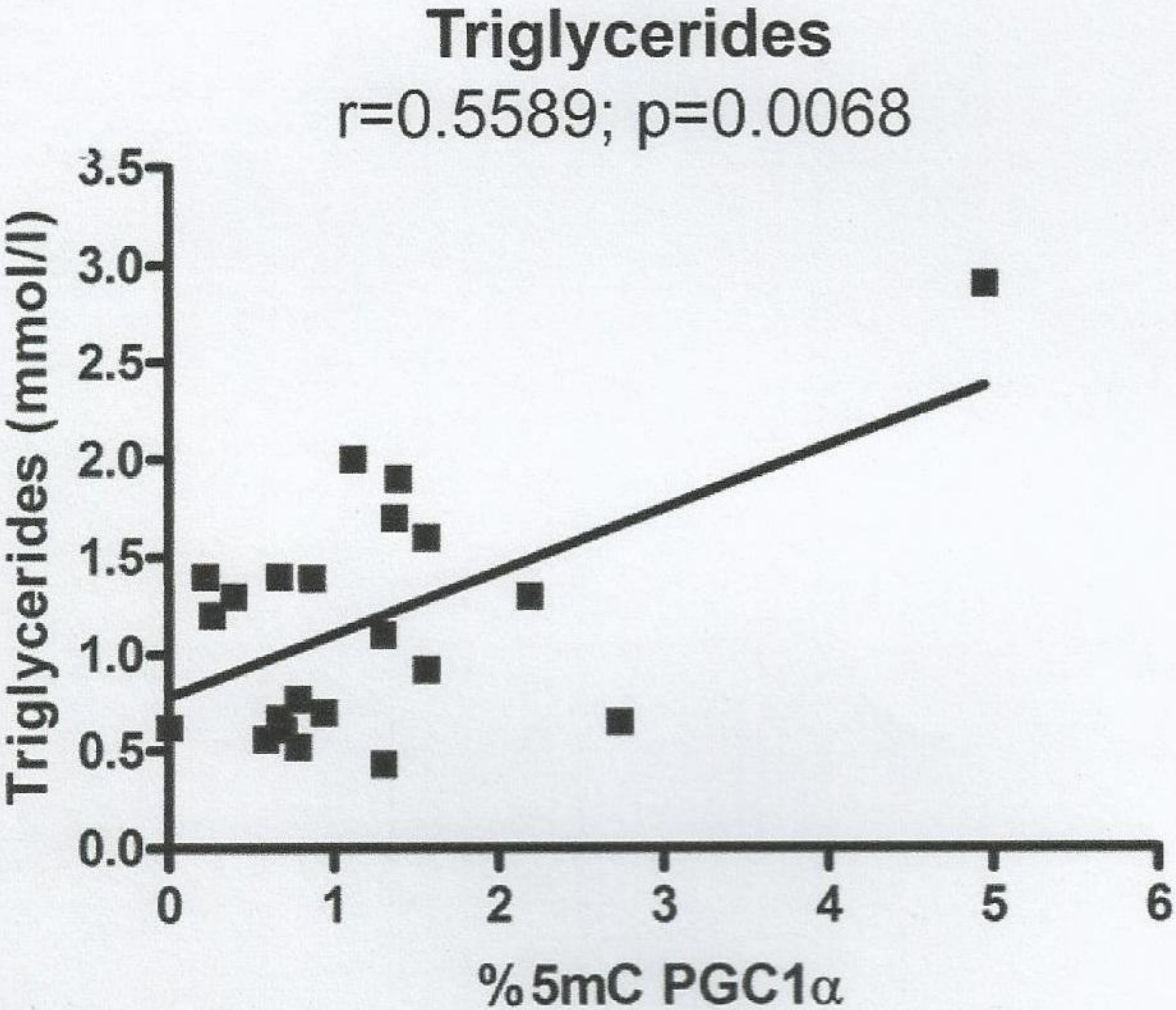
Cultured muscle cells maintain the "insulin resistant phenotype" of the donor, even after several passages

TNF-a and Free Fatty Acids Exposure Induce Acute Methylation of the PGC-1a Promoter

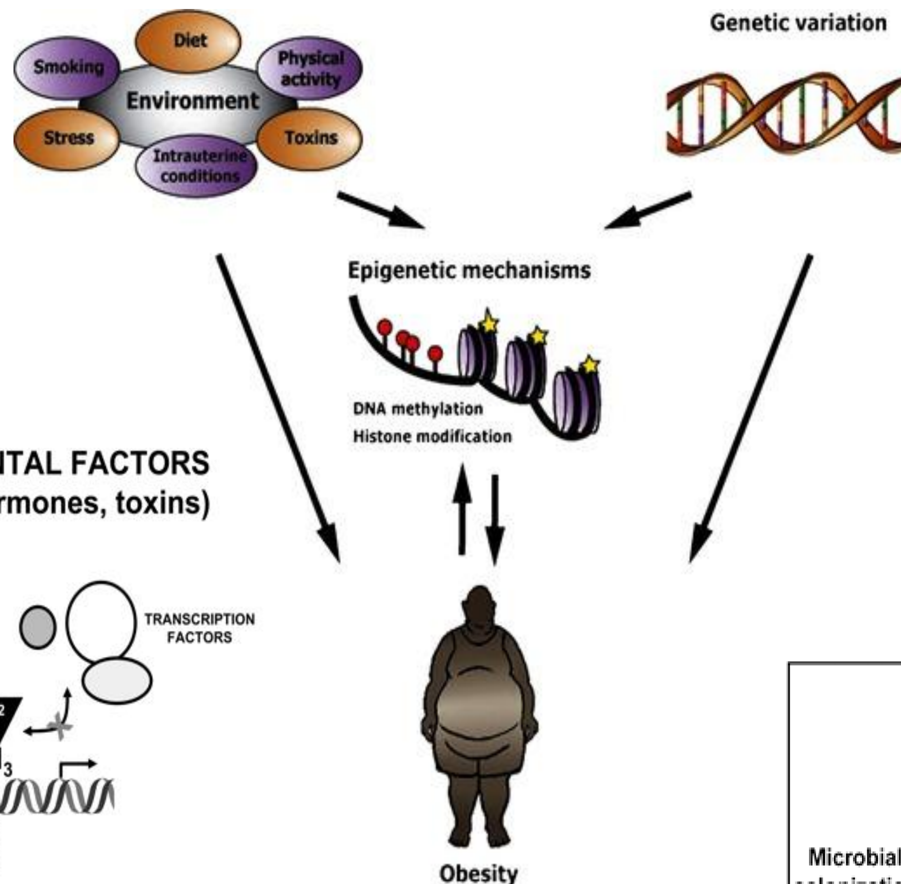


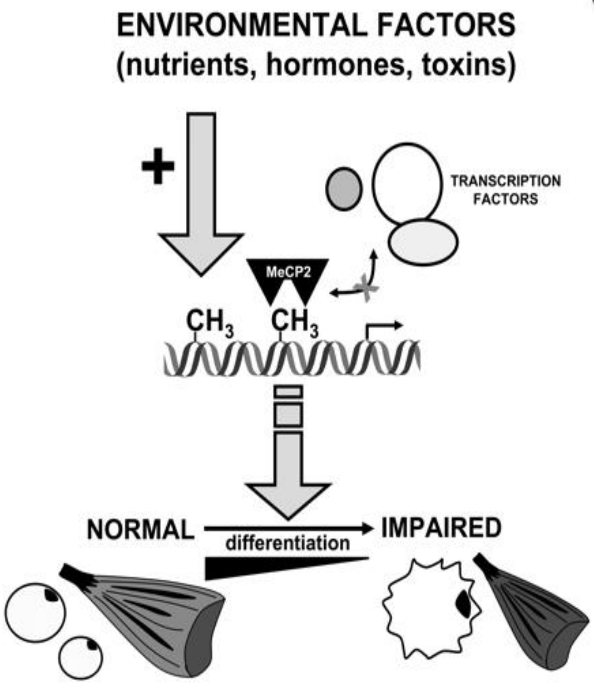
Barrès et al. Cell Metabolism 2009

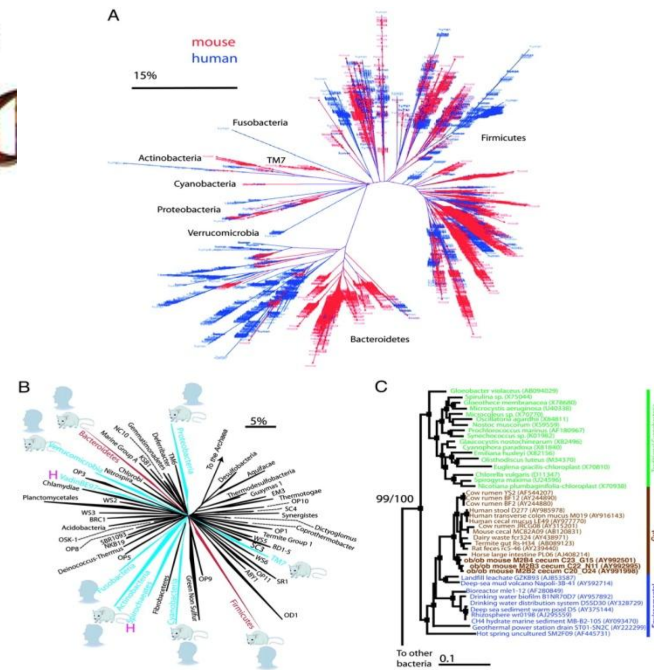
PGC-1α PROMOTER METHYLATION IS ASSOCIATED WITH TRIGLYCERIDE LEVELS

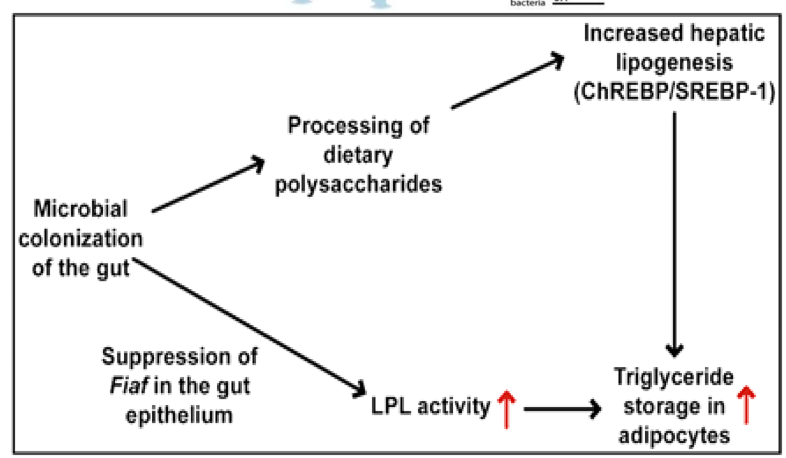


OBESITY & EPIGENETICS

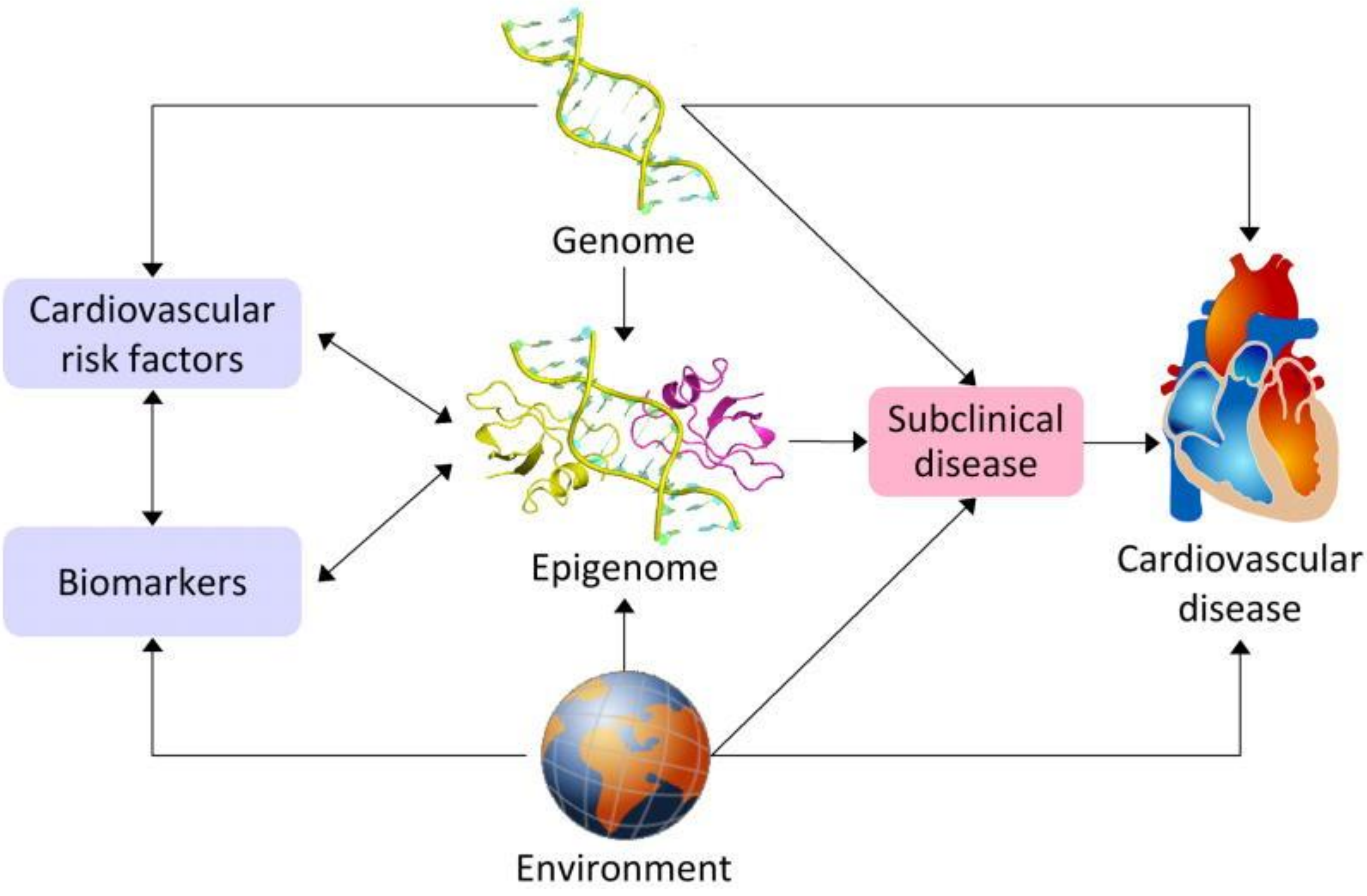




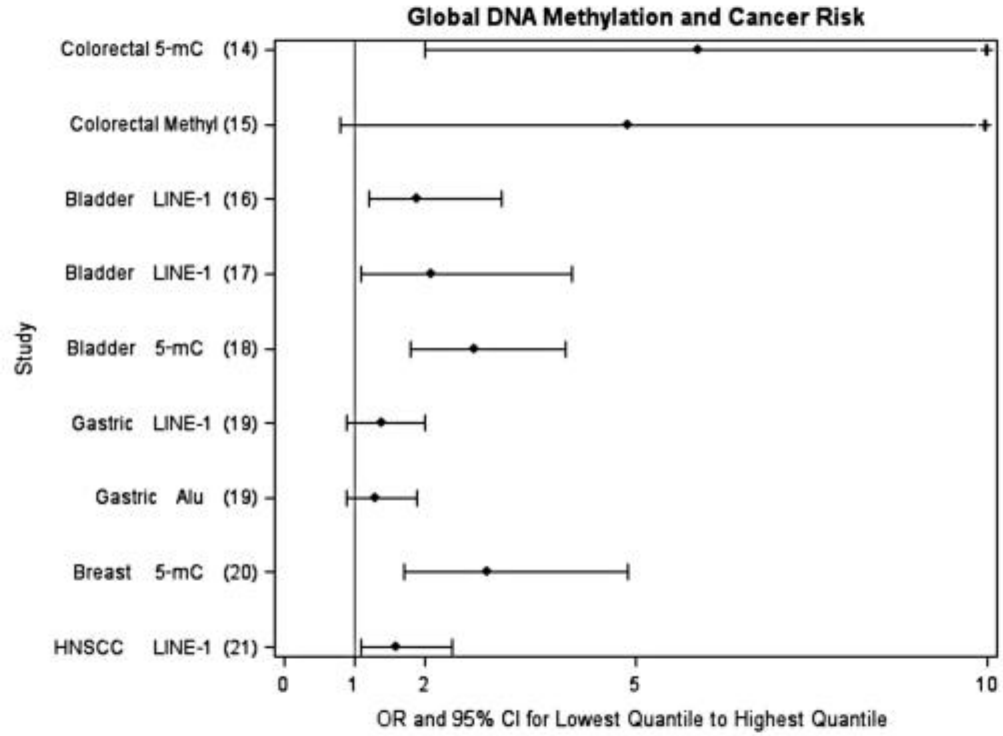


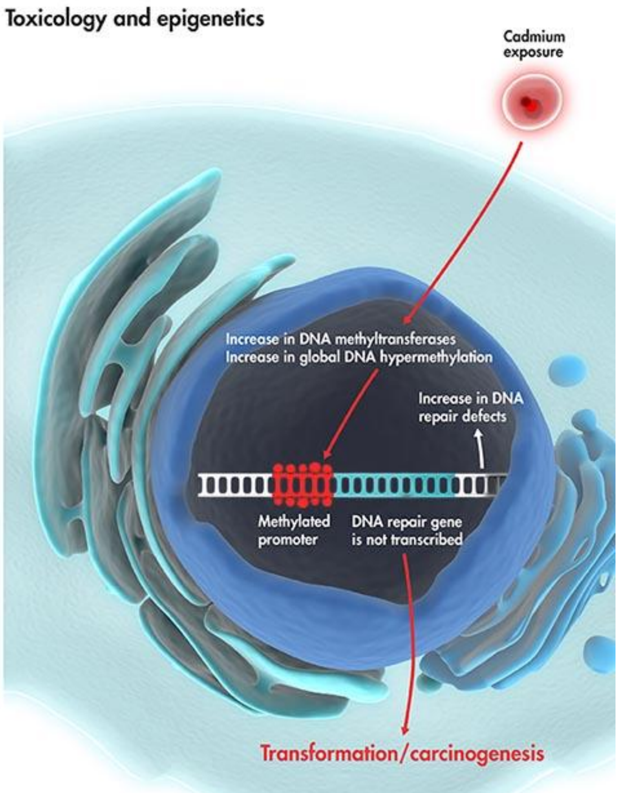


Cardiovascular epigenetics



CANCER & EPIGENETICS

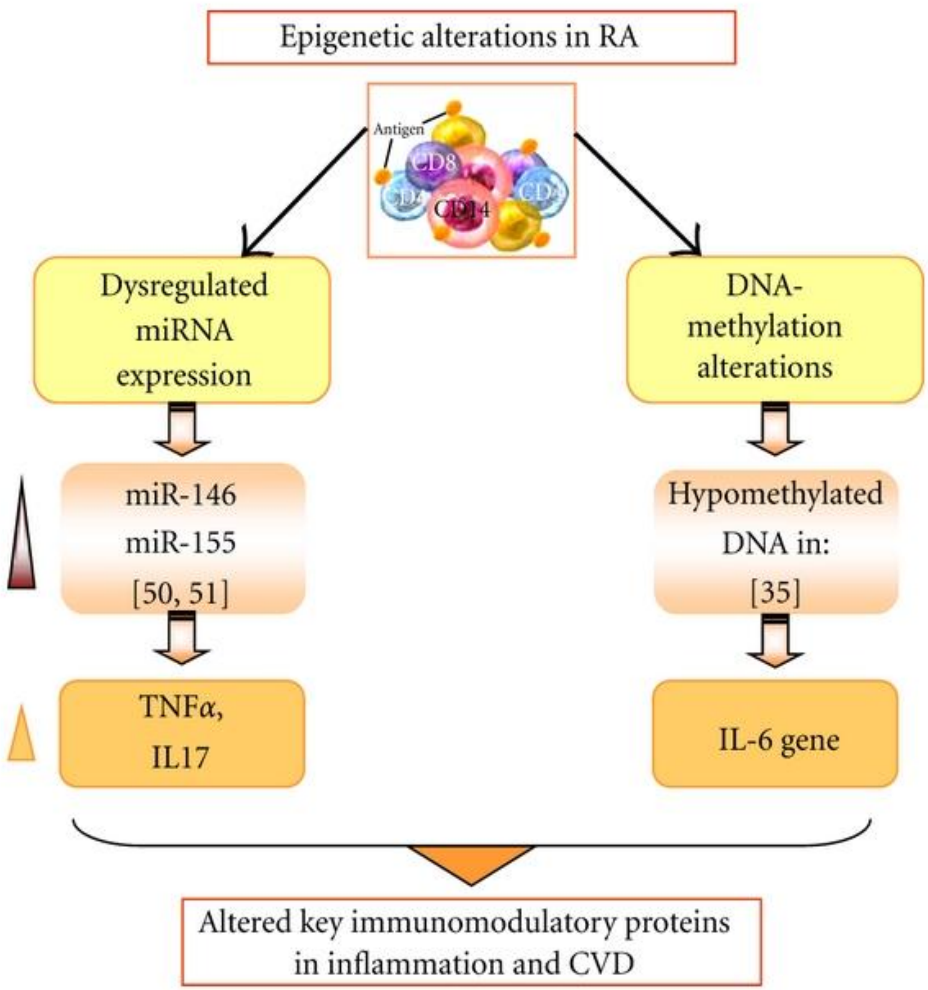


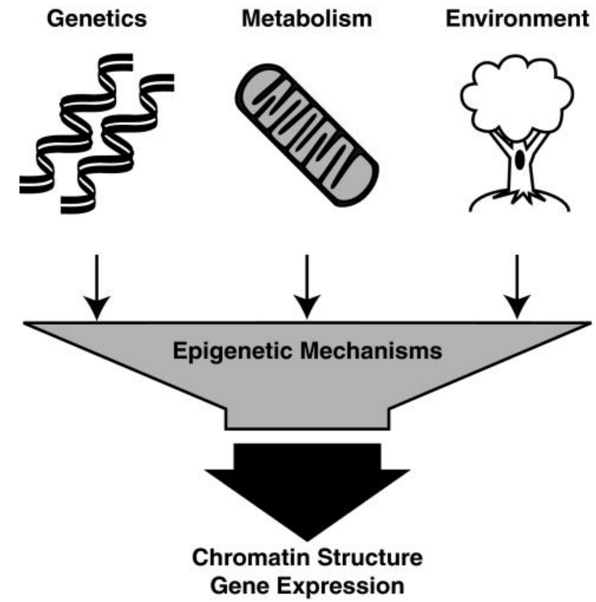


DNA methylation in white blood cells:
association with risk factors in epidemiologic studies.

Epigenetics. 2011 Jul;6(7):828-37. Epub 2011 Jul 1.

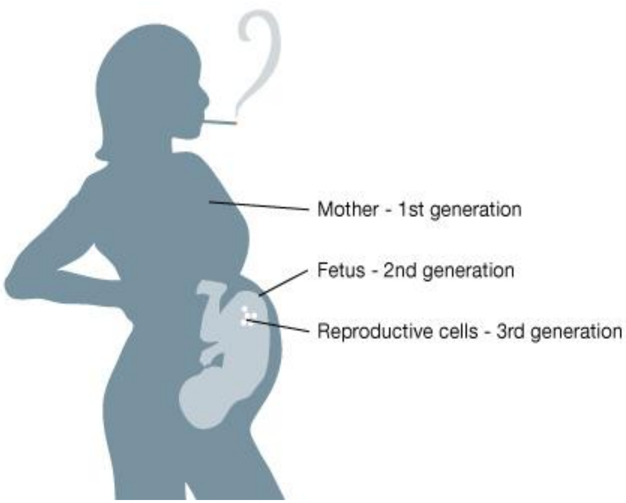
REUMATOID ARTHRITIS & CVD

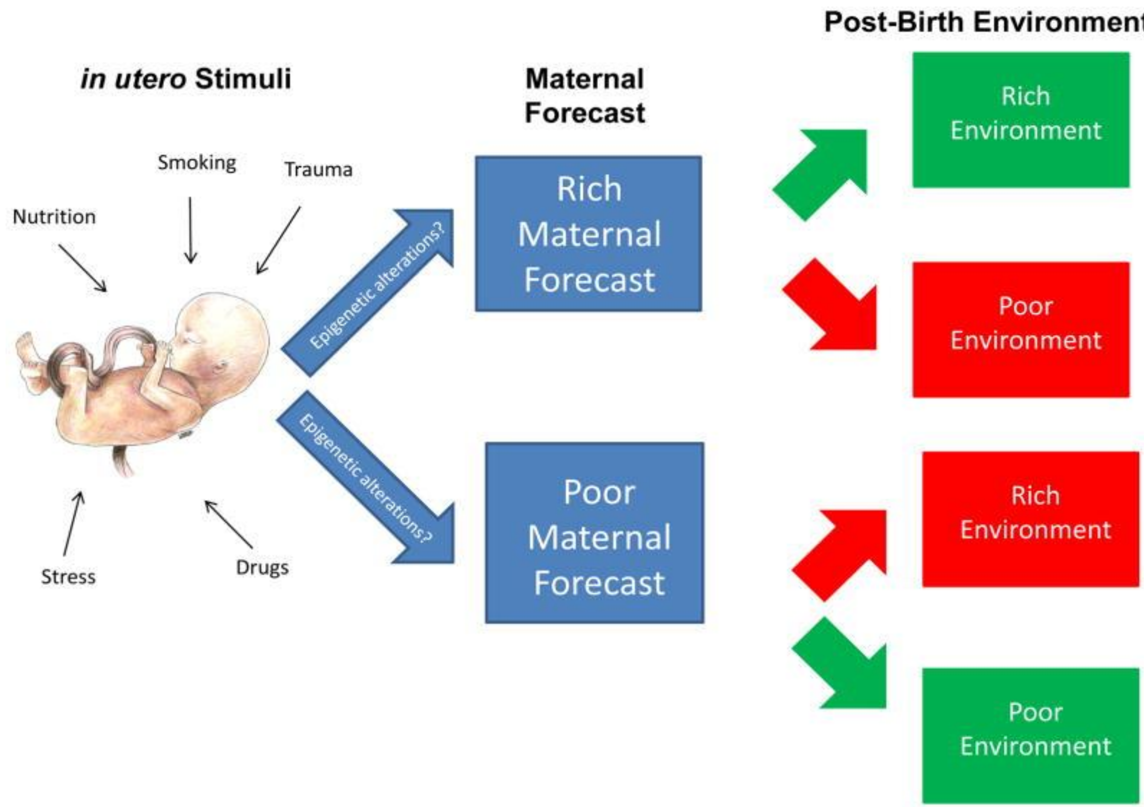




Clin Dev Immunol. 2012;2012:974648. doi: 10.1155/2012/974648. Epub 2011 Sep 14.

PERINATAL SMOKING EXPOSURE





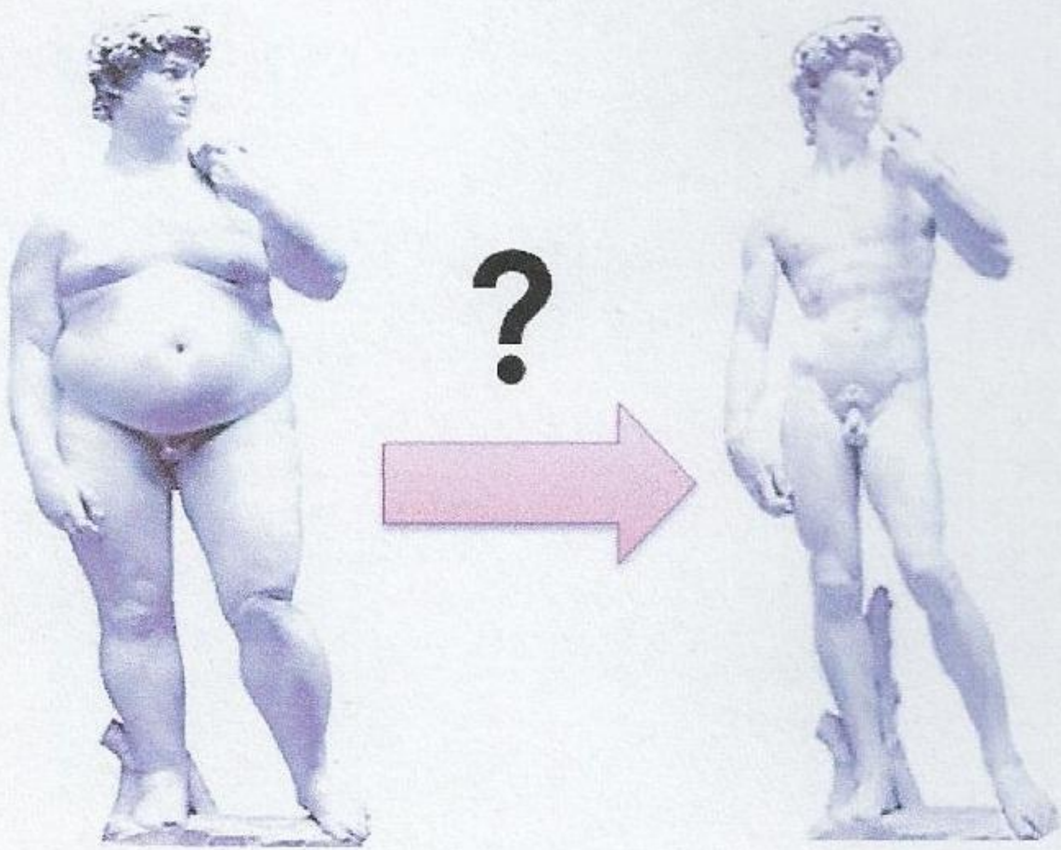
reduced birth weight

poor developmental and psychological outcomes

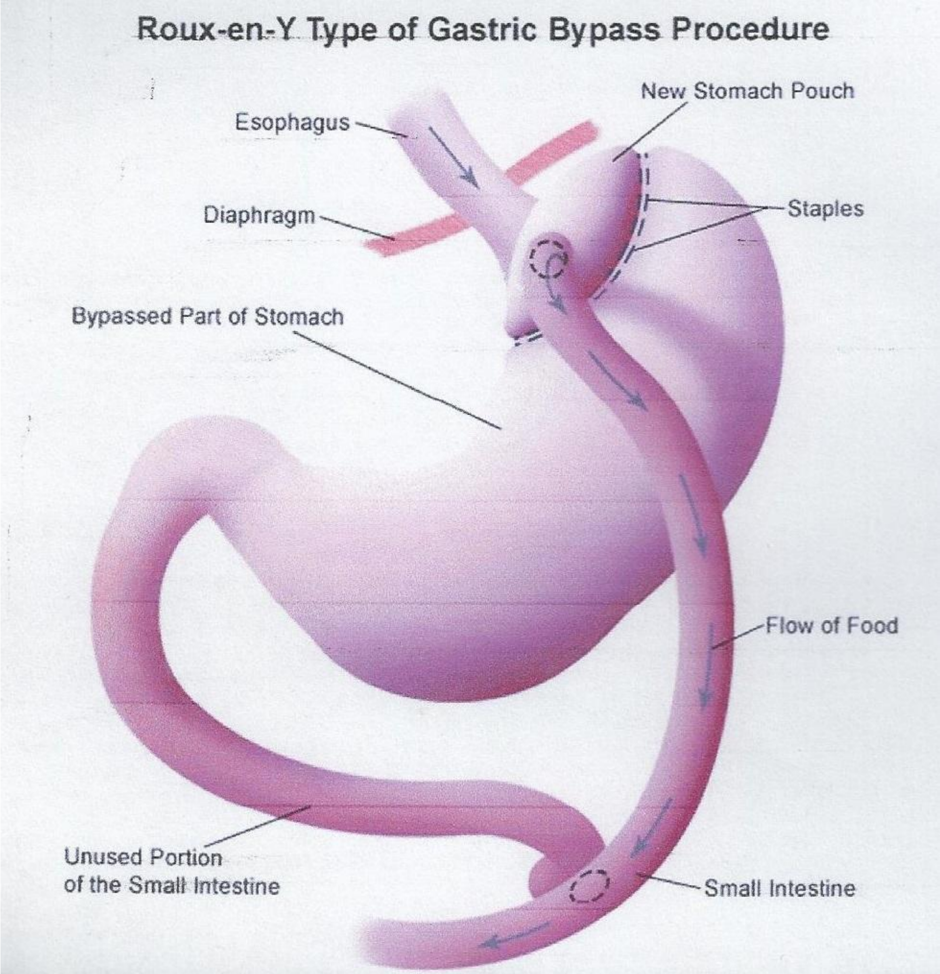
increased risk for diseases

behavioral disorders later in life

DOES WEIGHT LOSS REMODELS DNA METHYLATION PROFILE?



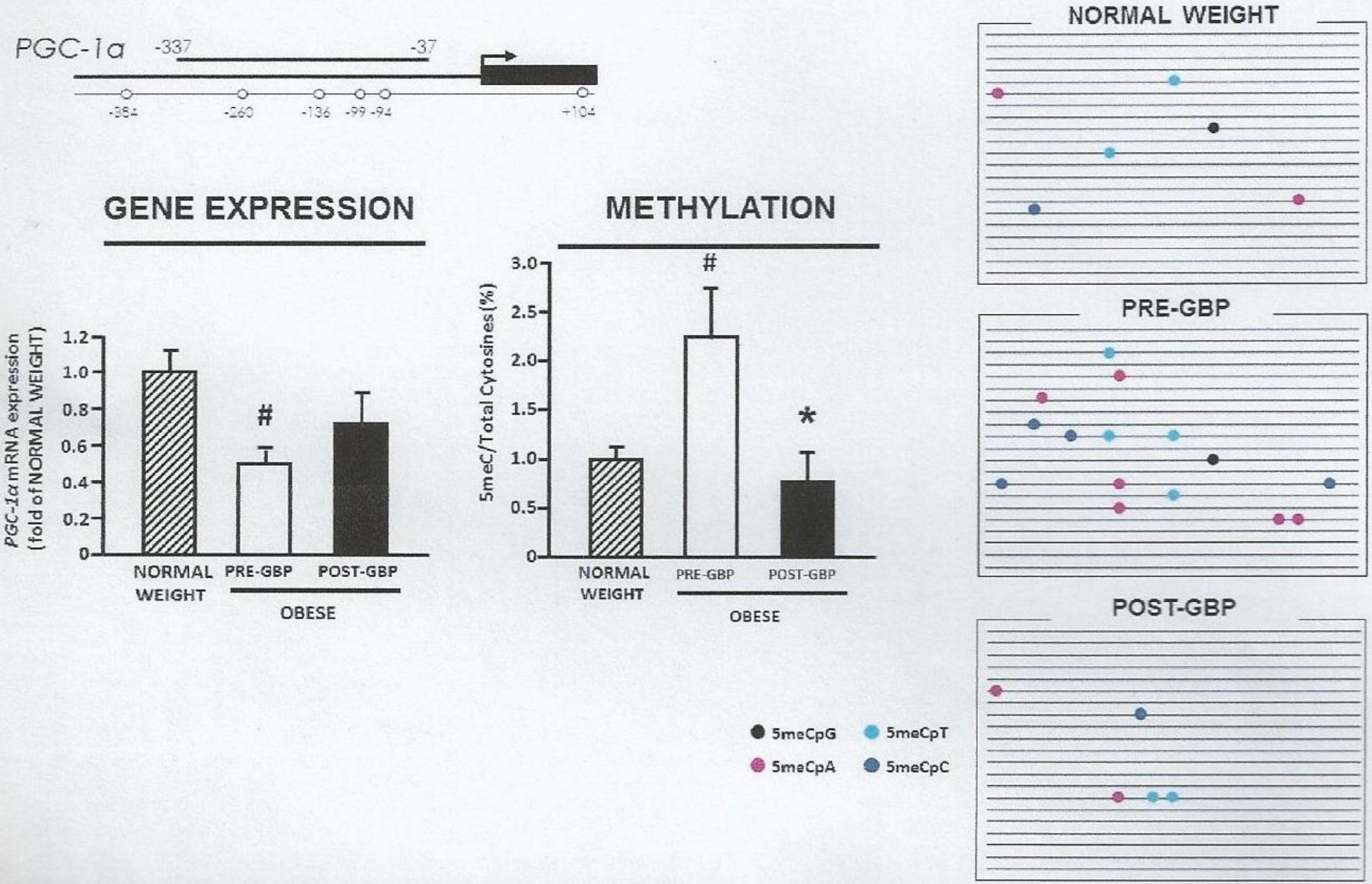
BARIATRIC WEIGHT LOSS



Loss of 30 kg

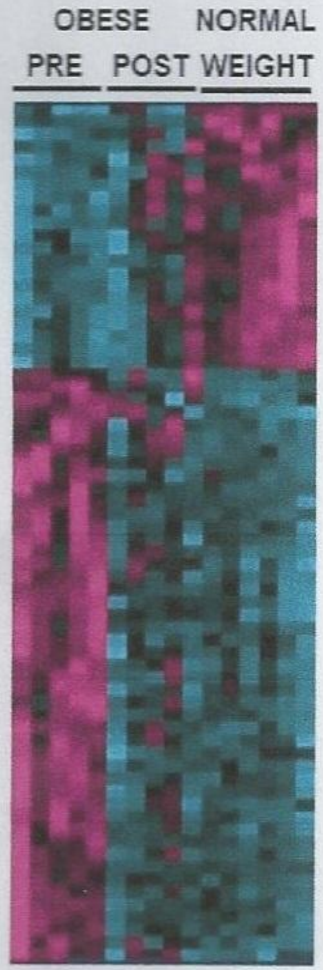
4 mo

OBESITY-ASSOCIATED ALTERED *PGC-1α* PROMOTER METHYLATION IS REVERSED BY WEIGHT LOSS

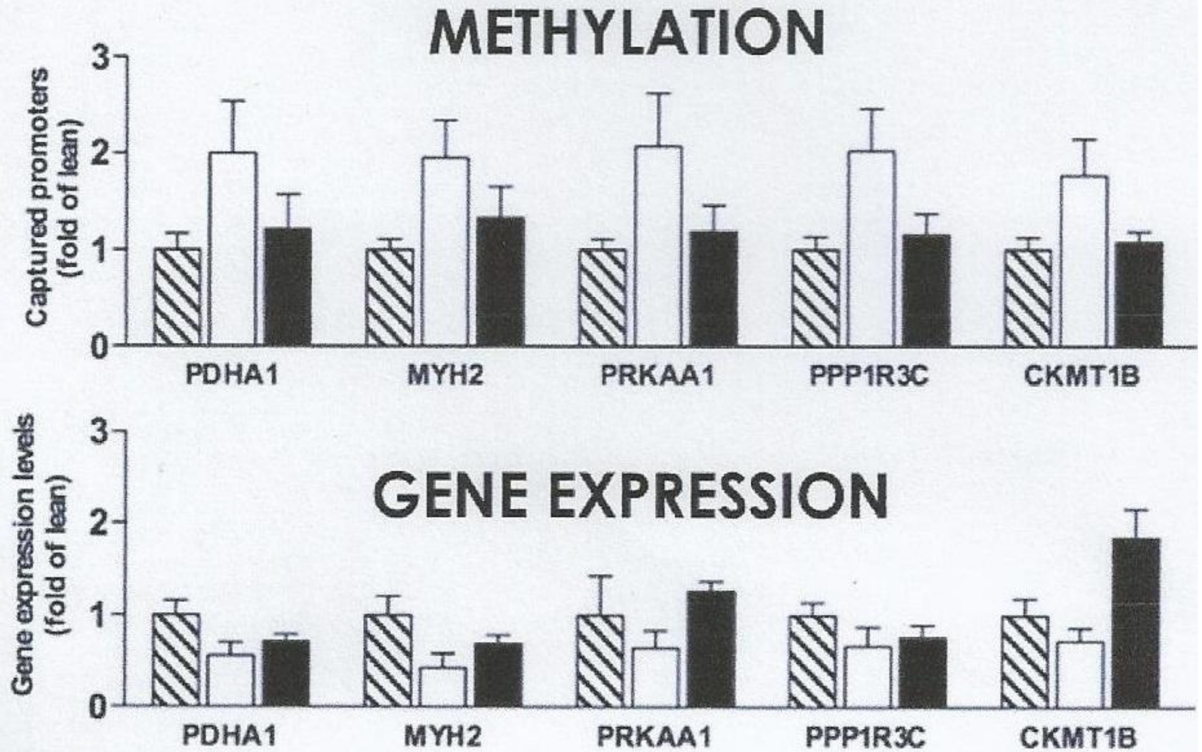


OBESITY-ASSOCIATED ALTERED DNA METHYLATION PROFILE IS REVERSED BY WEIGHT LOSS

Transcriptomics



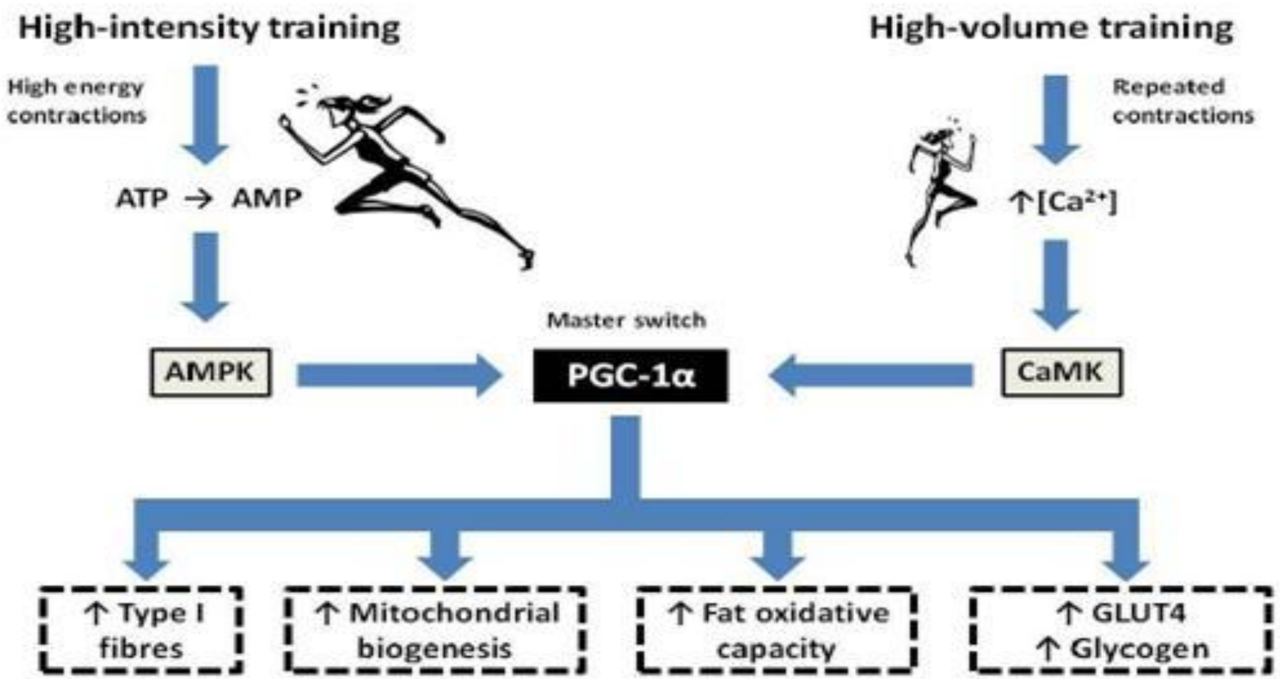
Gene specific analysis



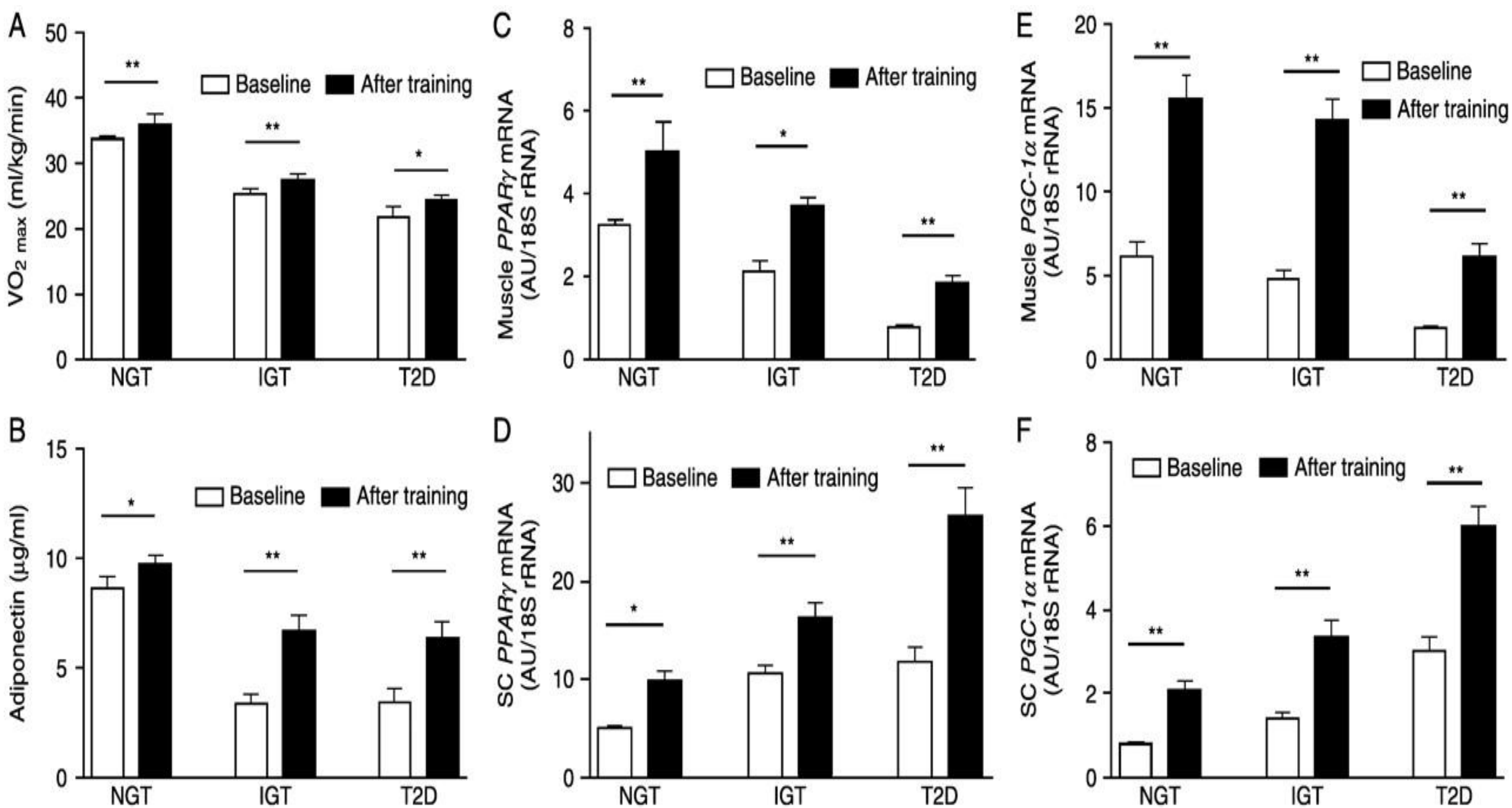
DOES EXERCISE REMODELS DNA METHYLATION PROFILE

PGC1a & ΑΣΚΗΣΗ

Figure 2.

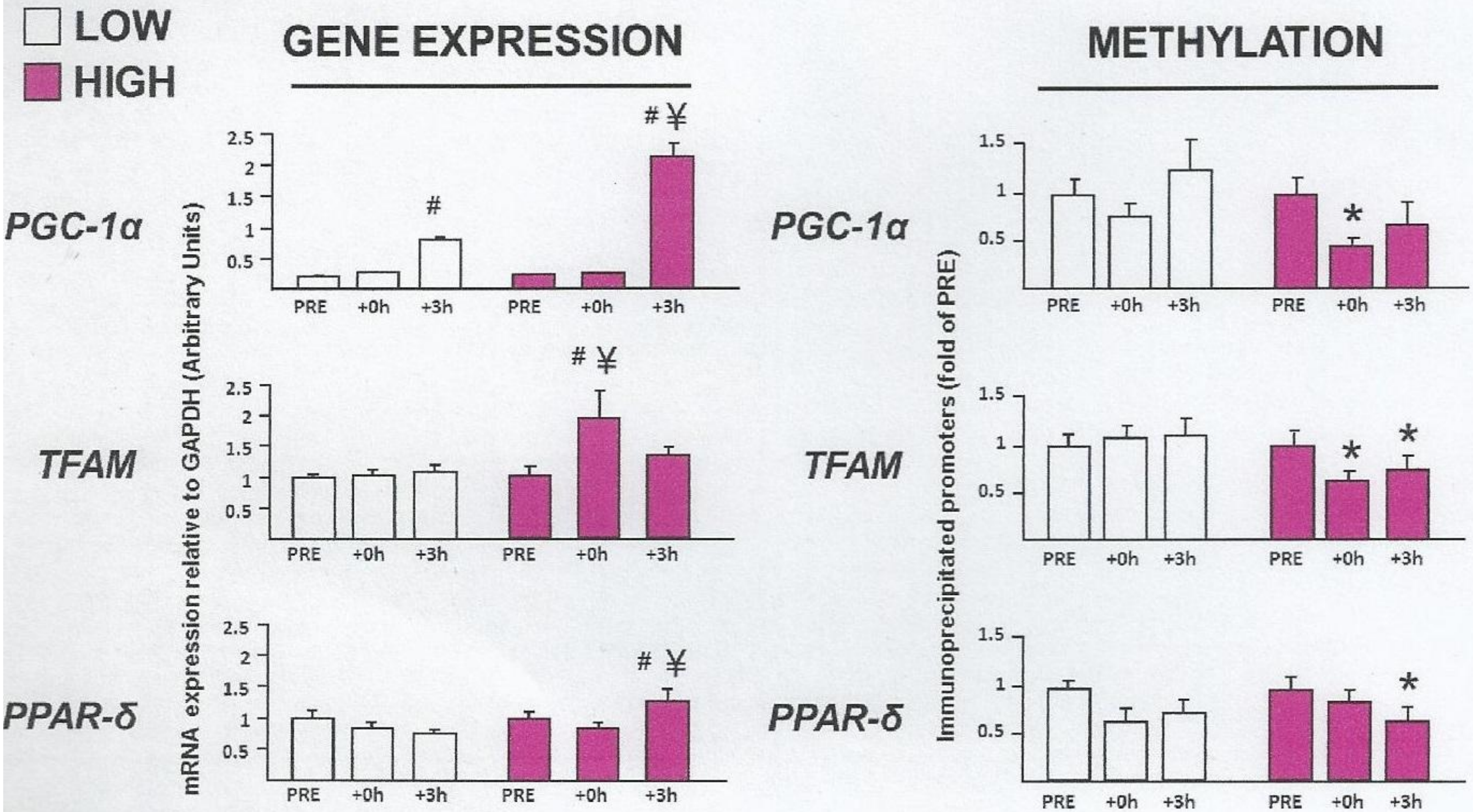


Effect of 4 w of exercise on skeletal muscle & adipose tissue PPARγ & PGC-1α in normal glucose-tolerant (NGT) and in IGT or type 2 diabetes (T2D).



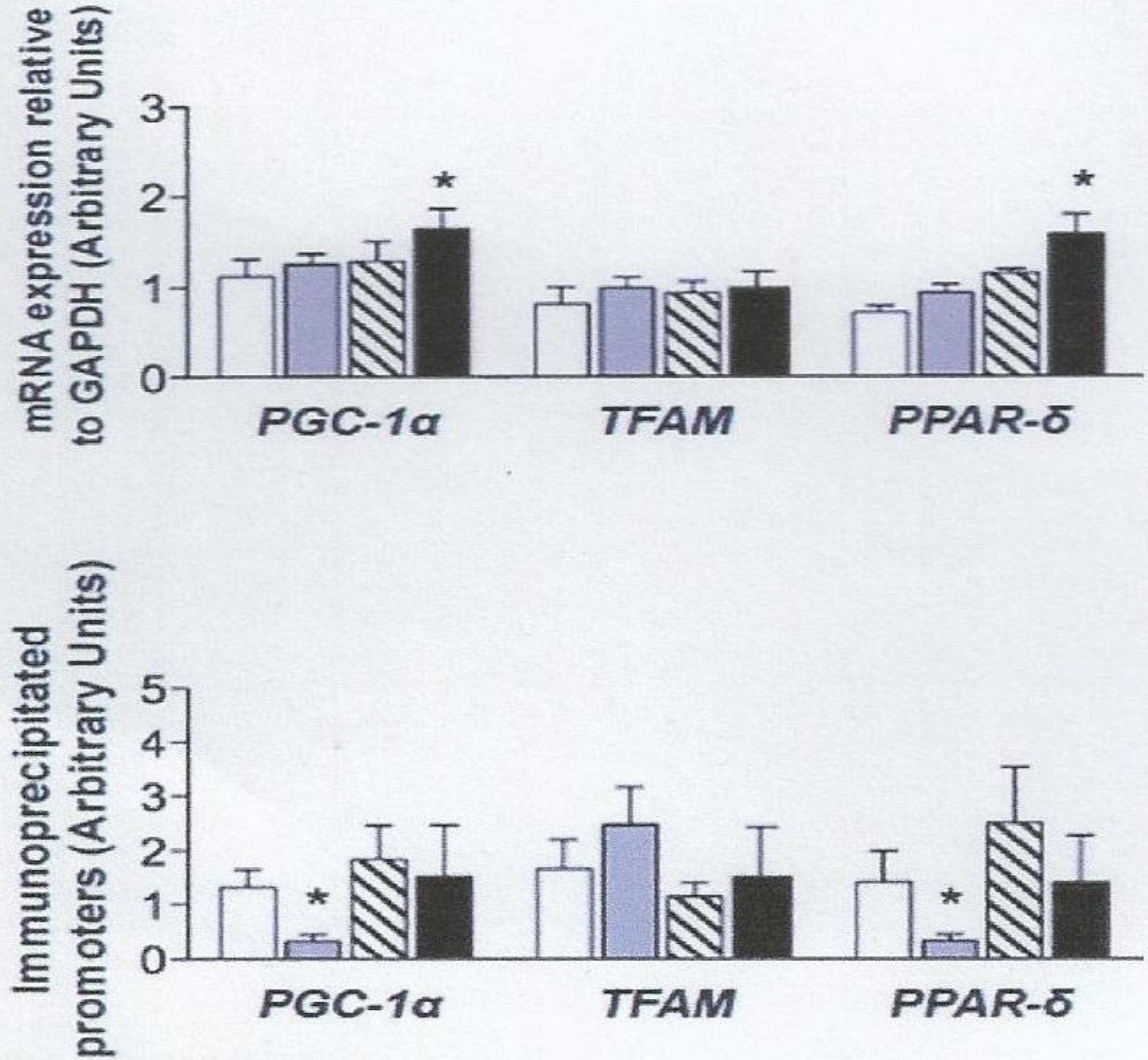
Published by BioScientifica

TIME-COURSE AND EXERCISE INTENSITY ANALYSIS OF DNA METHYLATION AND GENE EXPRESSION

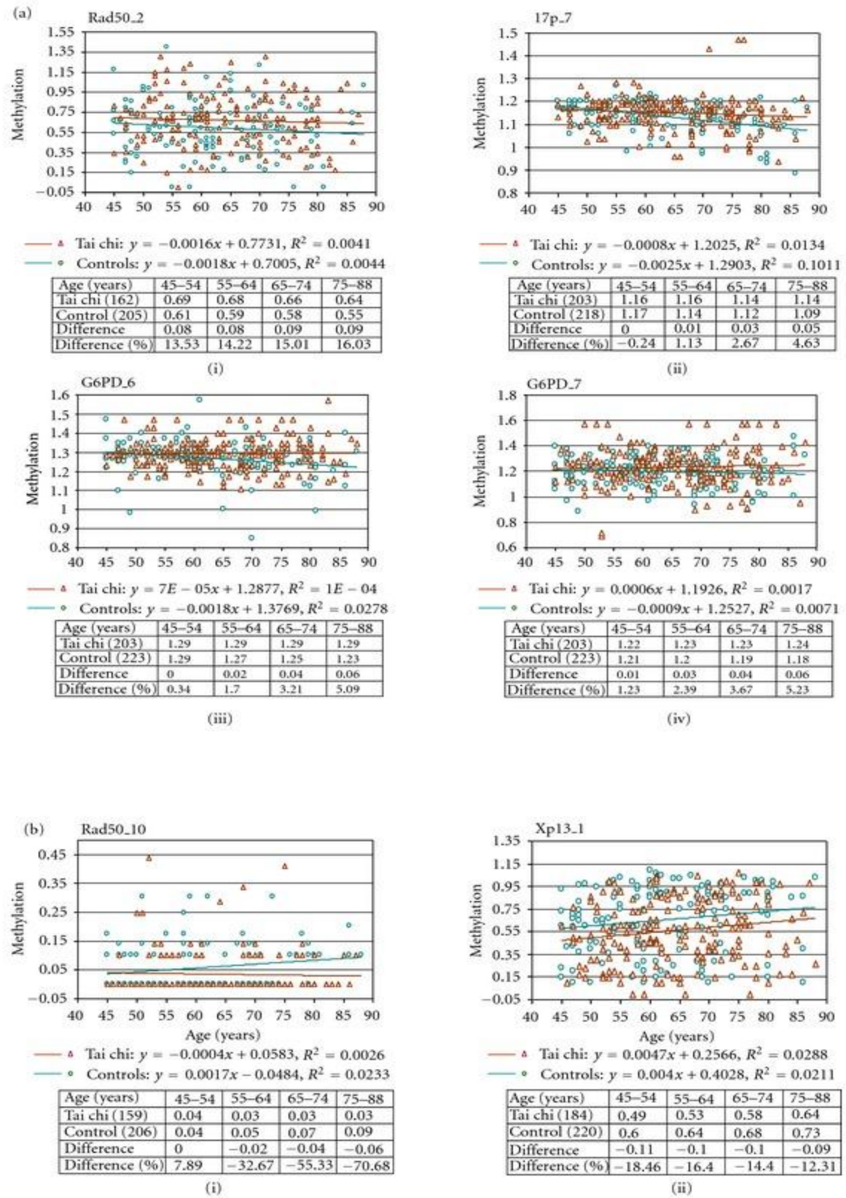


Inverse relationship between mRNA expression and promoter methylation

MUSCLE CONTRACTION INDUCES PROMOTER HYPOMETHYLATION

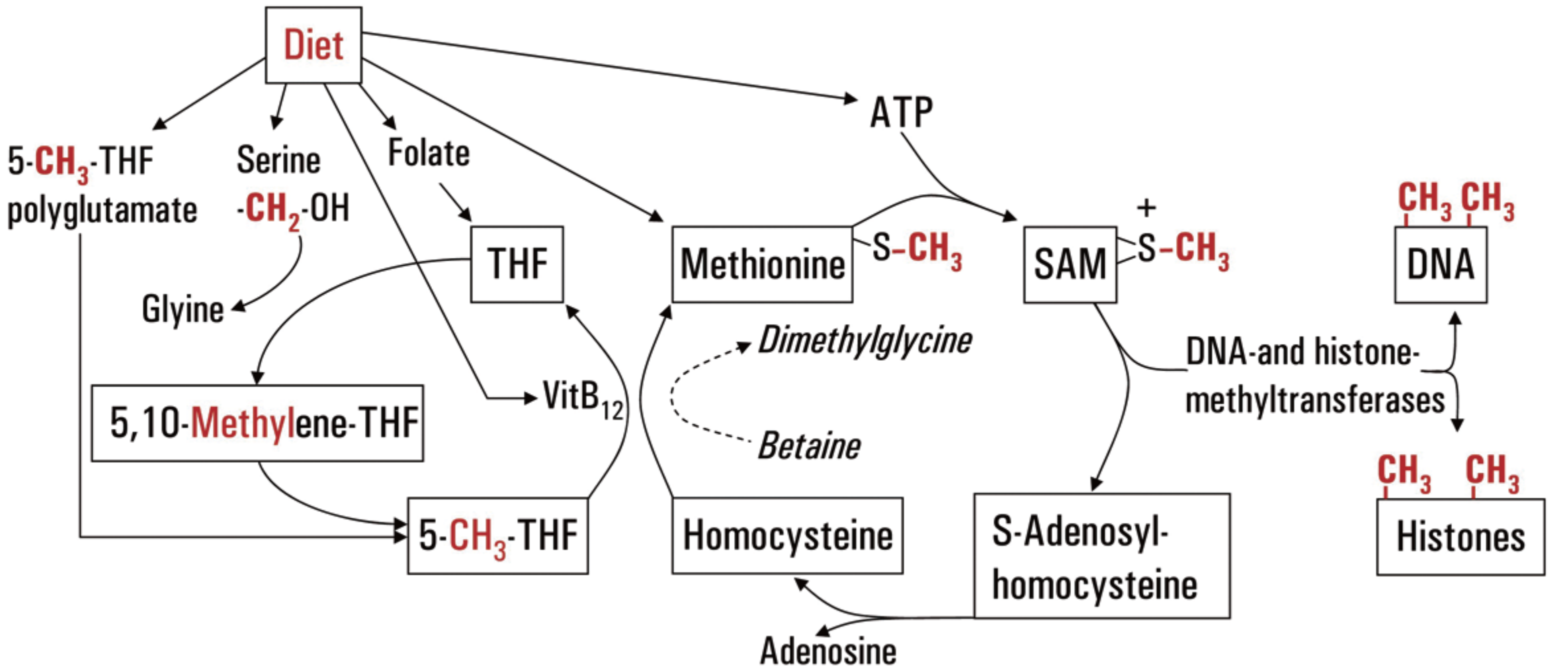


TAI CHI



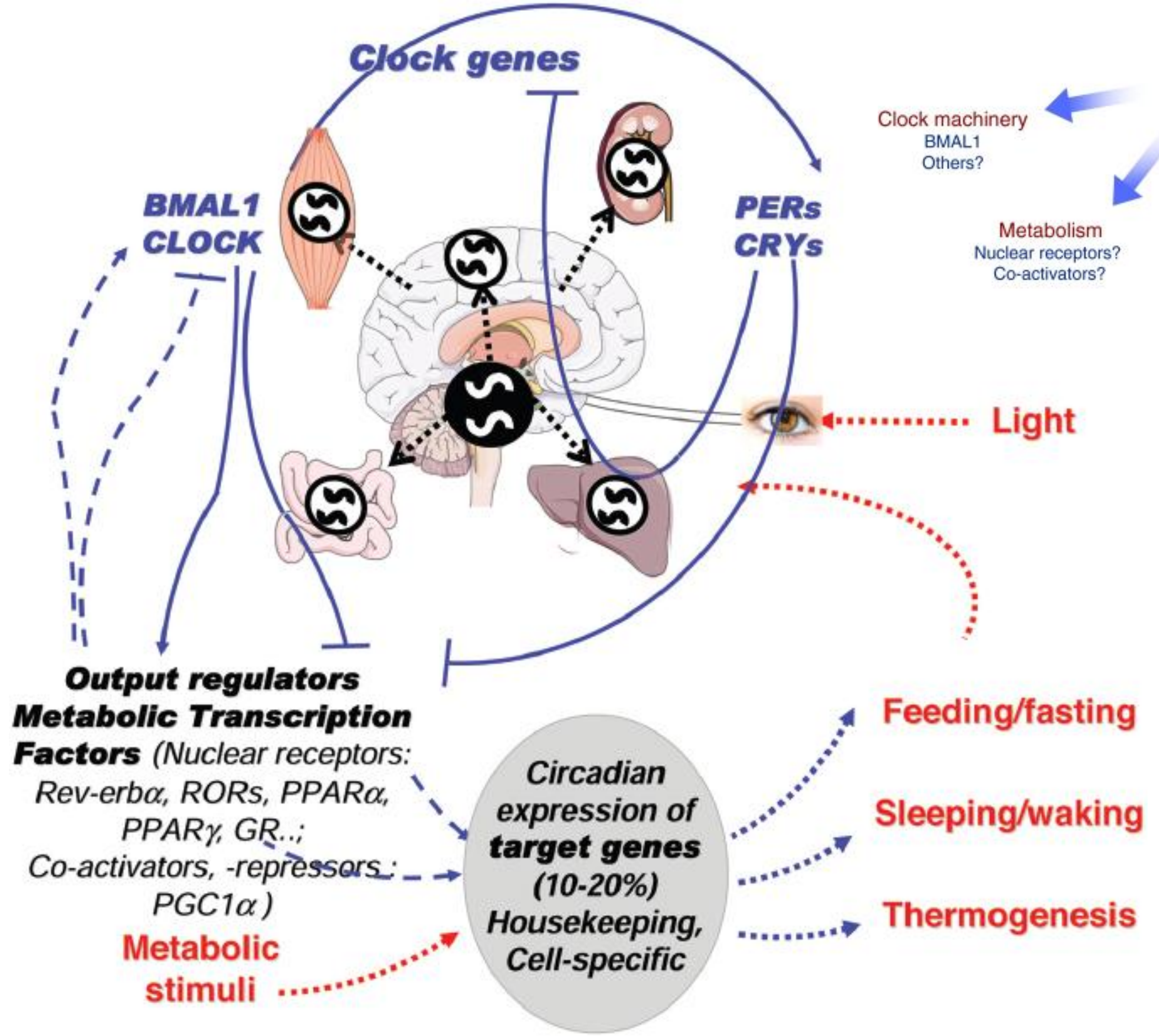
Evid Based Complement Alternat Med. 2012; 2012: 841810.

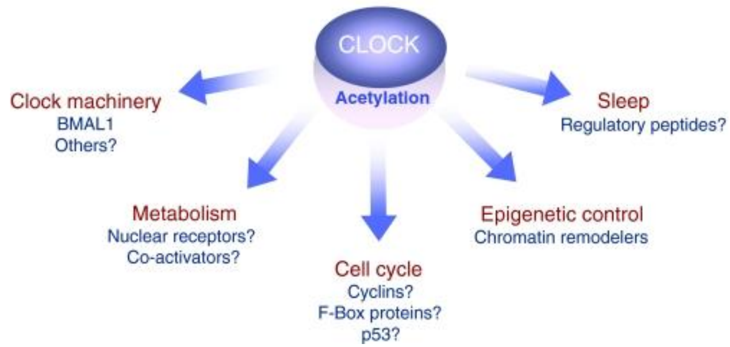
Epigenetic aspects of post-traumatic stress disorder



Disease Markers 30 (2011) 77–87 77

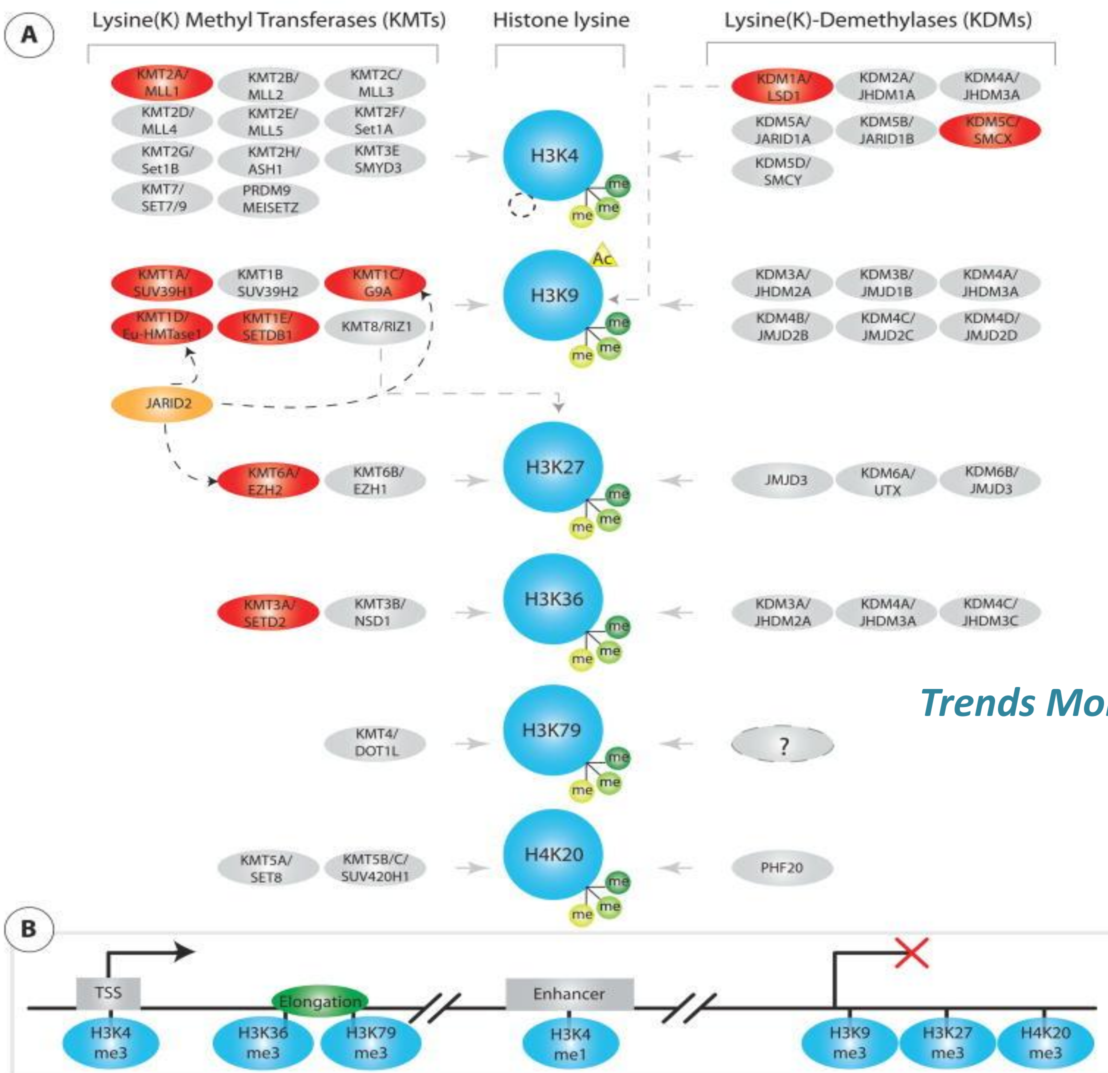
DIURNAL METHYLATION
CIRCARDIAN RHYTHM & CHRONOTHERAPEUTICS





J Cell Sci. 2010 Nov 15;123(Pt 22):3837-48

Balancing histone methylation activities in psychiatric disorders

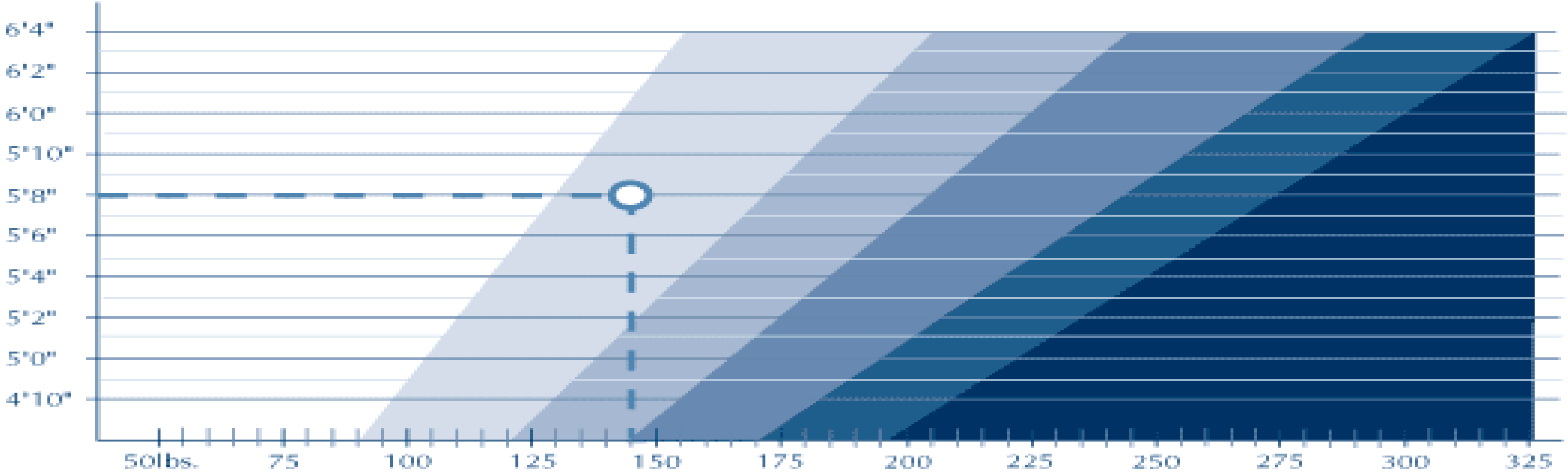


Red marked KMT/KDM are implicated in neurodevelopment or psychiatric disease

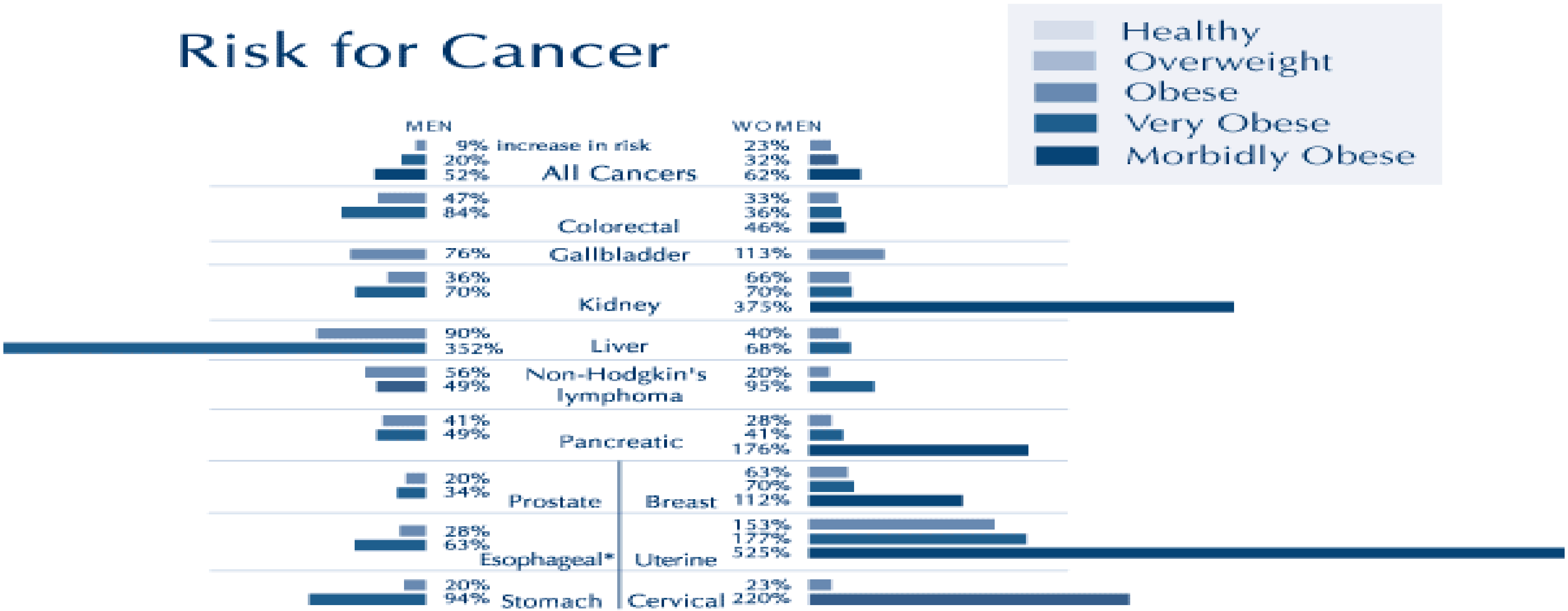
Trends Mol Med. 2011 17(7): 372–379.

Simplified scheme for selected mono- and trimethylated histone lysine

More Pounds, More Cancers

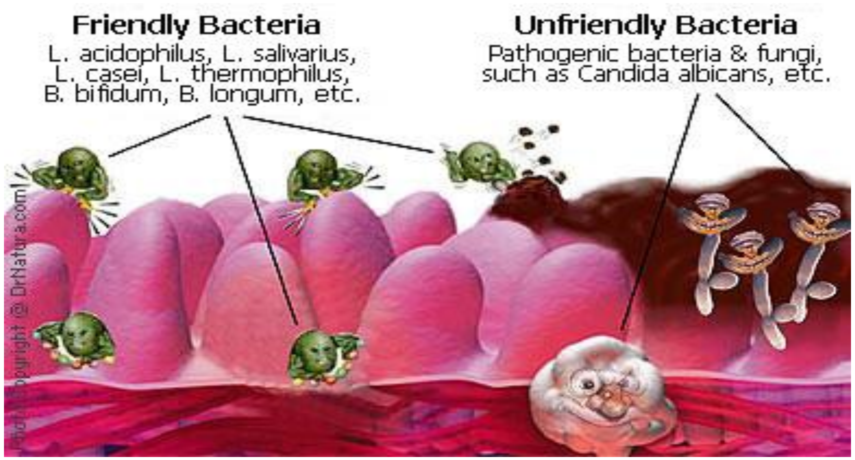


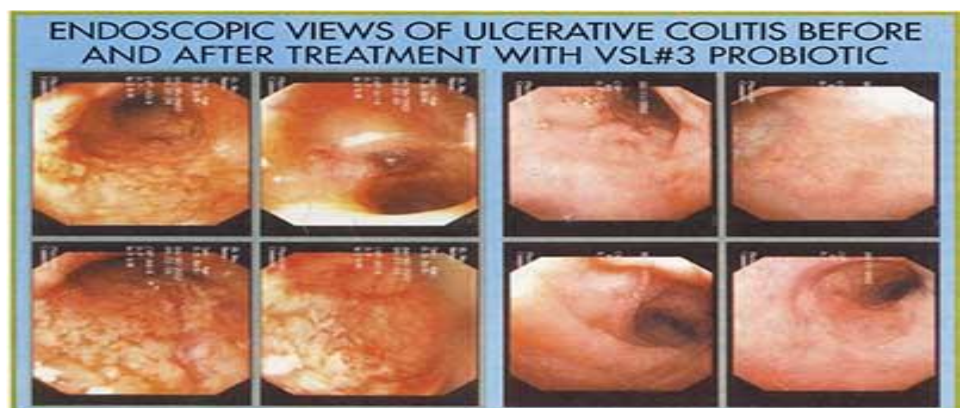
Risk for Cancer



Int J Obes Rel Metab Disord, 2003, 27:1447-52

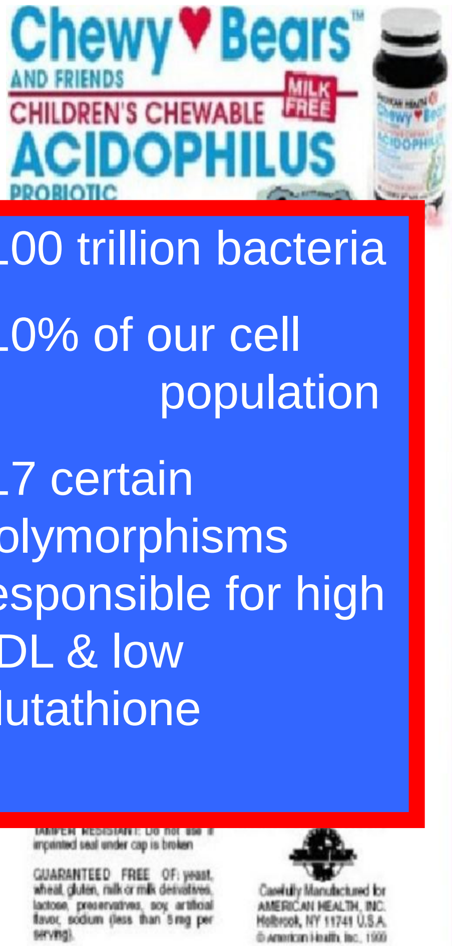
BACTERIA & HEALTH





THE FOUR IMAGES TO THE LEFT ARE BASELINE ENDOSCOPIC VIEWS FROM A PATIENT WITH ULCERATIVE COLITIS WHO DID NOT RESPOND TO CONVENTIONAL DRUG THERAPY. THE IMAGES TO THE RIGHT ARE FROM THE SAME PATIENT AFTER SIX WEEKS OF TREATMENT WITH THE VSL#3 PROBIOTIC COMBINATION. IMAGES REPRINTED WITH PERMISSION OF RICHARD FEDORAX, MD, UNIVERSITY OF ALBERTA.

MICROBIAL ENVIRONMENT & METABOLIC SYNDROM



- 100 trillion bacteria
- 10% of our cell population
- 17 certain polymorphisms responsible for high LDL & low glutathione

Recent changes in lifestyles have altered the human gut microbiome and linked disease patterns forever!

Special Biological Bandits:

Weird dietary fads
Antibiotic abuse
General drug popping
Western Post WW2 Diet
Dietary supplements

Exotic travel at an early age…exposures?
Immunological 'overprotection' of children?

… Is this really a good idea?

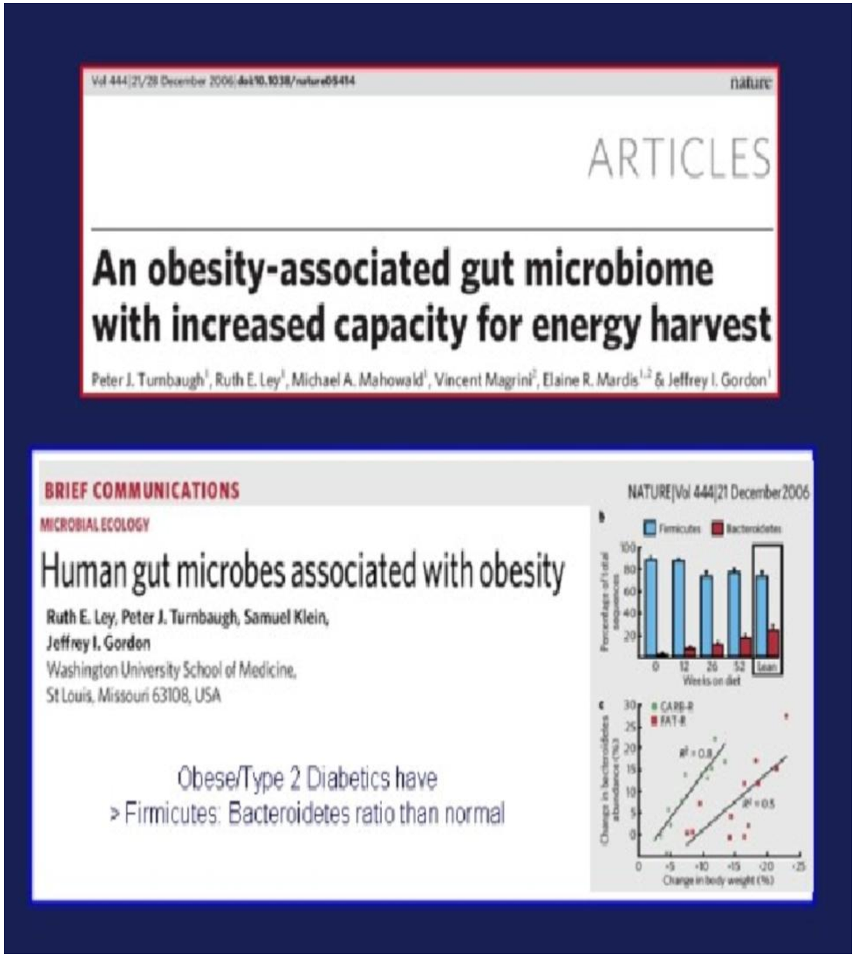
© Imperial College, 20

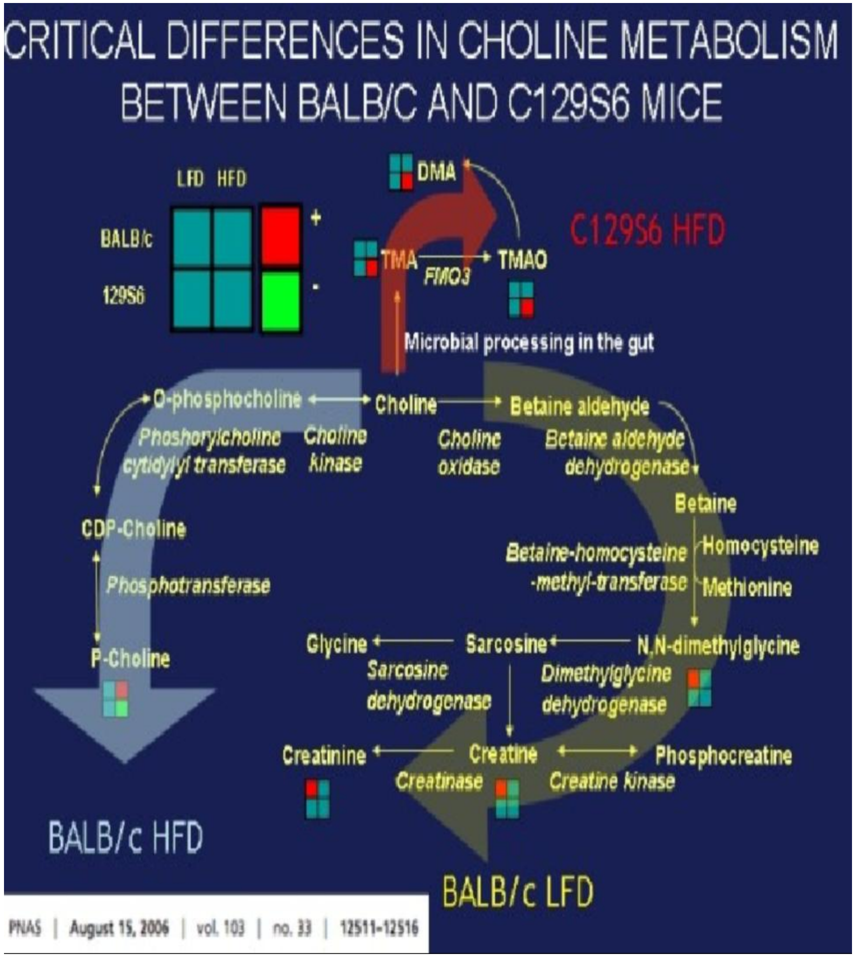
Some major 'non-infectious' human diseases and conditions with associated gut microbiotal disorders: All "modern" diseases.

Gastric ulcers (*Helicobacter pylori*) - Barry J Marshall & J Robin Warren (2005 Nobel Prize for Medicine)
Colonic cancer
Inflammatory bowel conditions
Ulcerative Colitis & Crohn's disease
Allergies & related immune disorders
asthma, eczema, psoriasis….
Insulin resistance related diseases- type 2 diabetes and obesity…
Many neuropsychiatric disorders….

© Imperial College, 2007

HOW HUMANS WE ARE?





EPIGENETICS

INFILTRATING

EVOLUTIONARY

REVERSAL

PROCCESS


Messages
Dad
Edit
Dad.... I got my girlfriend pregnant...
WHAT?!?!!?!?!?
Nah I'm just kidding. I just failed my Bio exam
OH THANK GOD!!!
Send