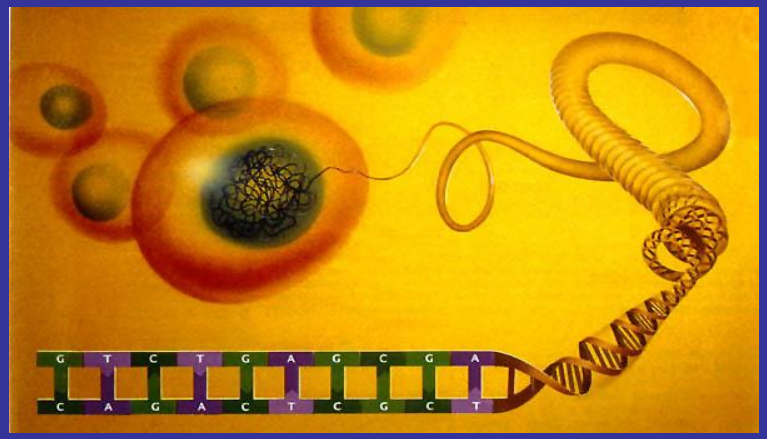
ΣΑΚΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ

ΠΡΟΣΕΓΓΙΣΗ ΣΤΗΝ ΠΑΘΟΦΥΣΙΟΛΟΓΙΑ ΜΕ ΤΗ ΜΟΡΙΑΚΗ ΒΙΟΛΟΓΙΑ



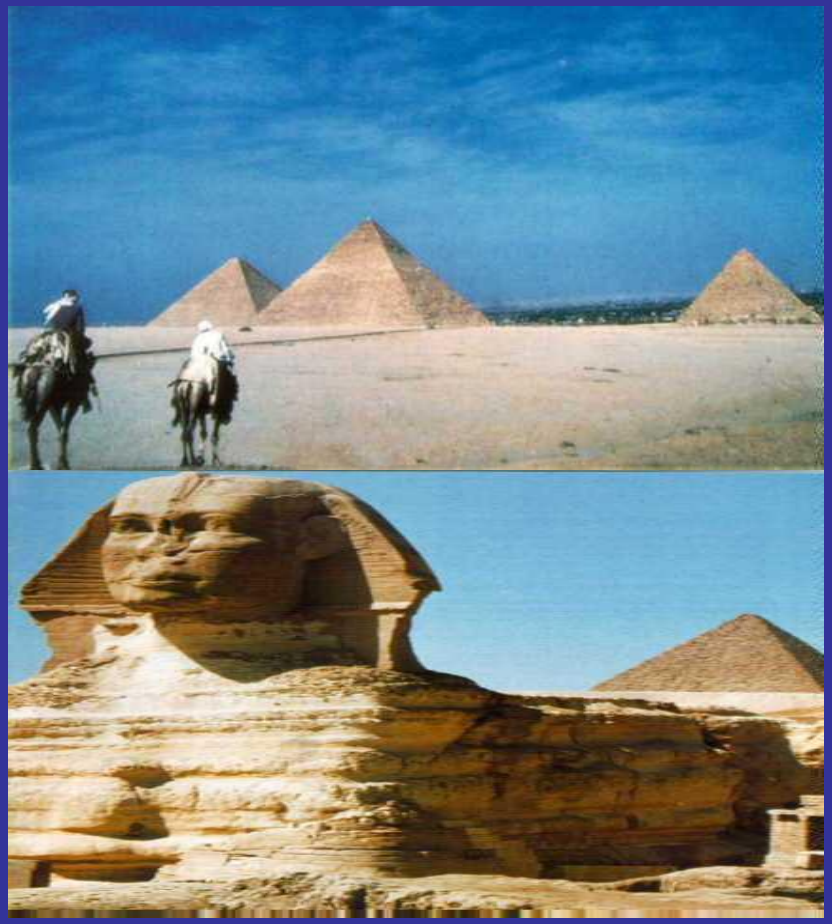
Π.Γ.ΧΑΛΒΑΤΣΙΩΤΗΣ

Επίκ.Καθηγητής

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

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝ.ΝΟΣΟΚΟΜΕΙΟ "ΑΤΤΙΚΟΝ"

ΜΙΑ ΦΟΡΑ ΚΑΙ ΕΝΑΝ ΚΑΙΡΟ……



Hesy Ra 1550 BC

ΕΠΙΠΤΩΣΗ ΤΟΥ ΔΙΑΒΗΤΗ

- 30.000.000 (1985)
- 194.000.000 (2003)
- 333.000.000 (2025)
- Αύξηση λόγω της βελτίωσης του προσδόκιμου επιβίωσης & της αλλαγής των προτύπων διαβίωσης

ATTICA study

overweight	obese
53% males	20% males
31% females	15% females

Cardiometabolic Syndrom

25.2%	males
14.6%	females

Panagiotakos D.B. et al, Am Heart J. 2004 Jan;147(1):106-12.

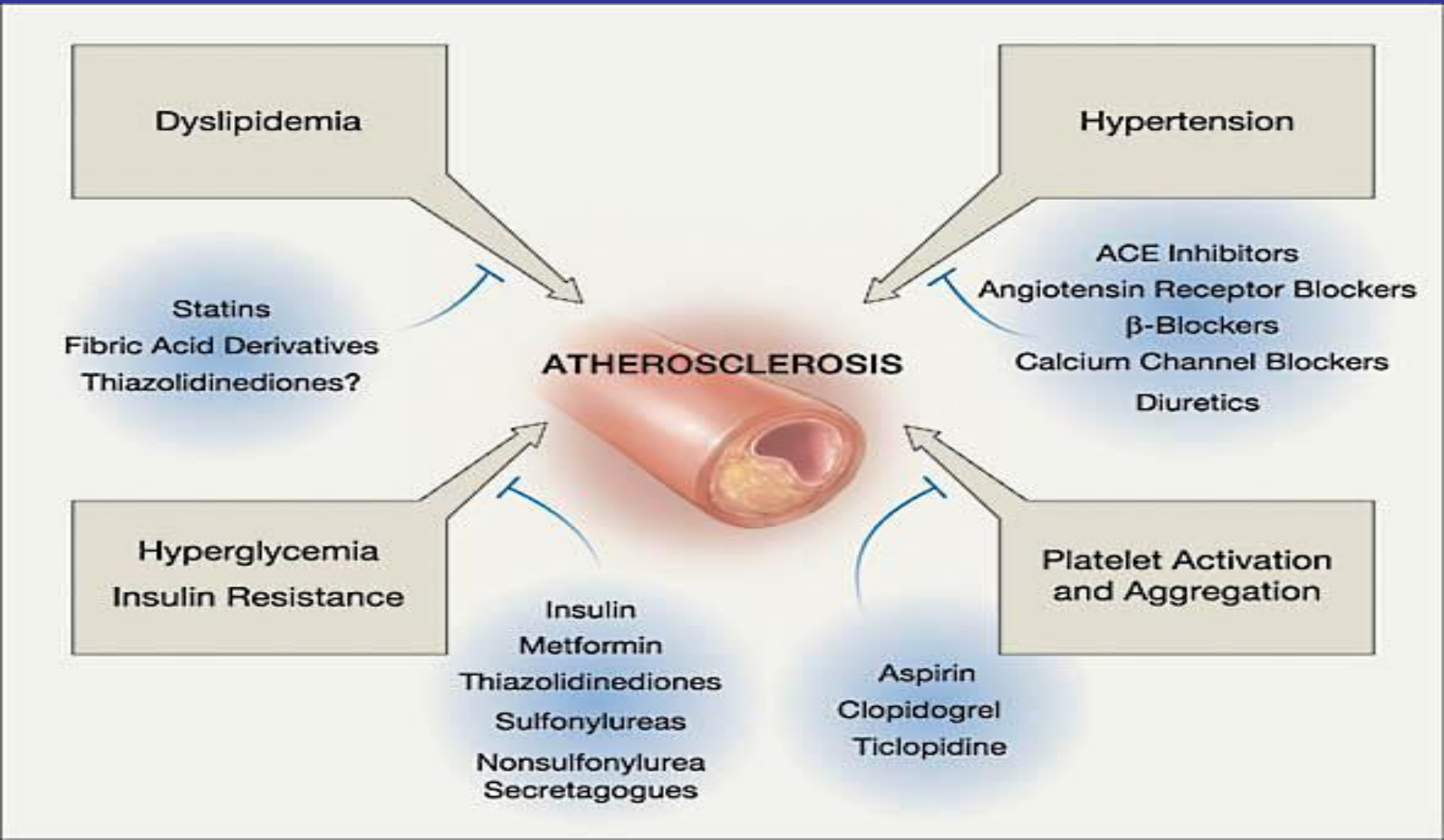
& Obes Res. 2004 Dec;12(12):1914-20.

Diabetes prevalence

Males	Females	Total	Egaleo study 1990
8.5 (%)	7.8 (%)	8.2 (%)	5.9(%)

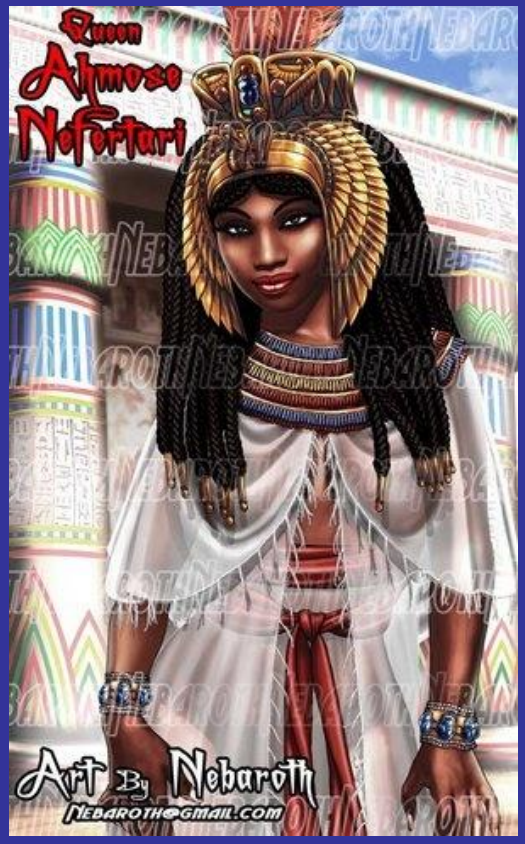
Gikas A et al in BMC Public Health. 2004 Feb 14;4(1):2

ΑΘΗΡΩΜΑΤΙΚΗ ΝΟΣΟΣ & ΜΕΤΑΒΟΛΙΚΟ ΣΥΝΔΡΟΜΟ



"Pharaoh Merenptah (*1213 -1203 BC*) died at age 60, he had atherosclerosis, arthritis and dental decay."

Allam AH et al, Computed Tomographic Assessment of Atherosclerosis In Ancient Egyptian Mummies JAMA 2009: 302(19)2091-4



20 ancient Egyptian mummies

high socio-economic position such as priests, court officials

died at an average age 45,

serious cardiovascular diseases

vascular calcifications observed in both males & females

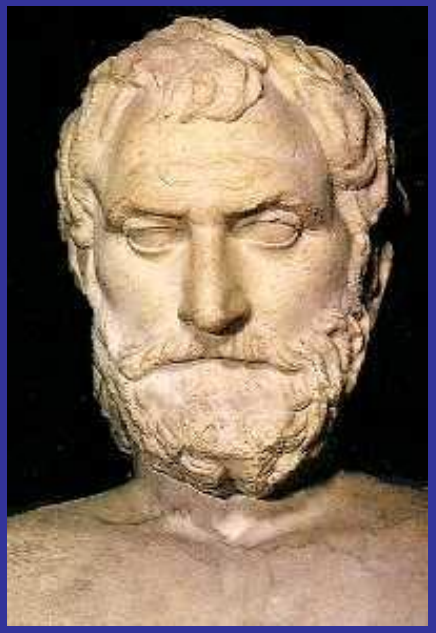
used salt to preserve food (increases blood pressure)

eating large amounts of bread, cheese, red meat and poultry as well as honey & cakes with butter, (increases cholesterol)

«THE GENE» HYPOTHESIS

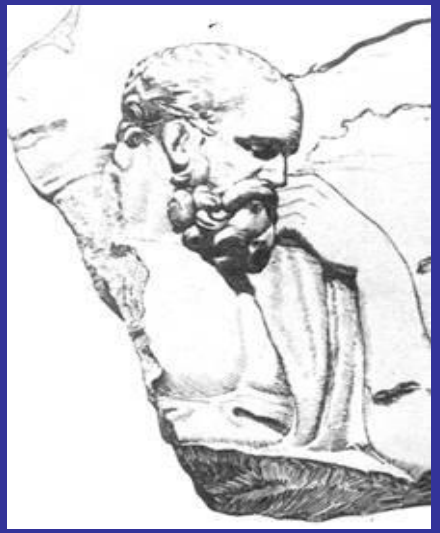
«all hereditary and genetic information exist in the sperm»

ANAXAGORAS
(500 - 428 B.C.)

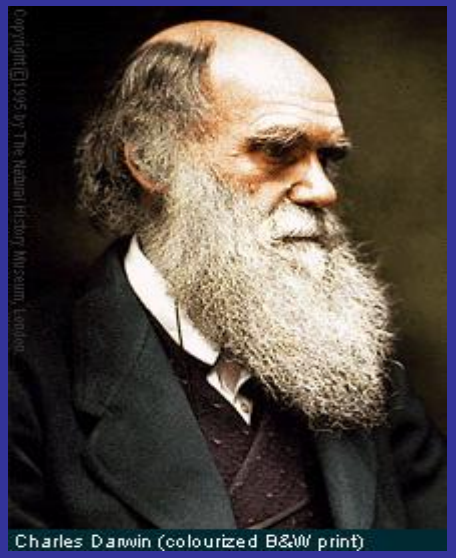


«species evolution theory»

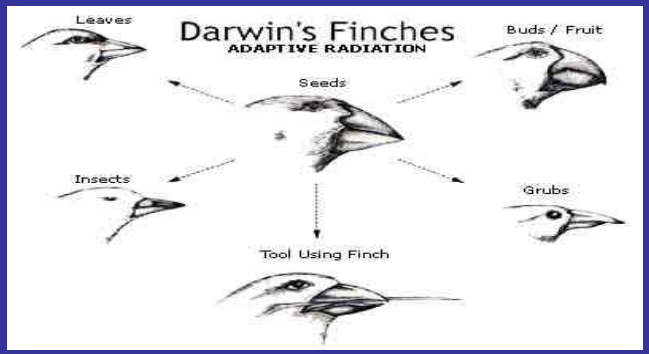
ANAXIMANDROS
(611-546 B.C.)



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

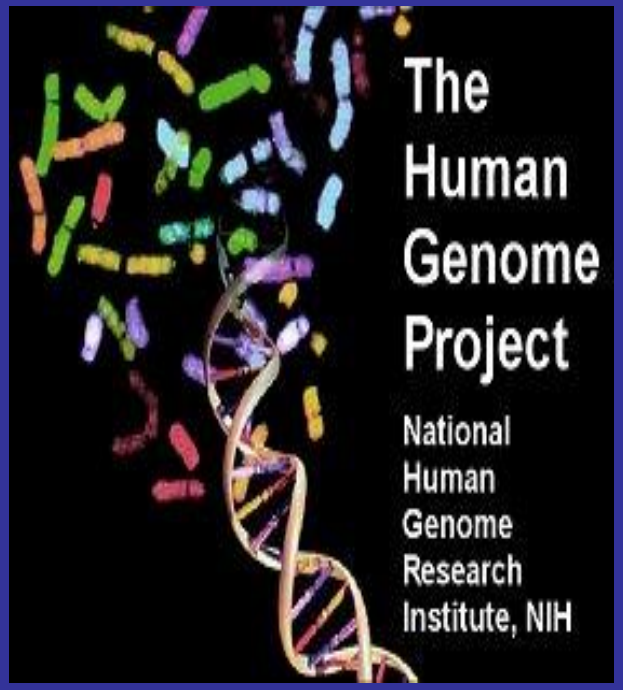


1809 - 1882

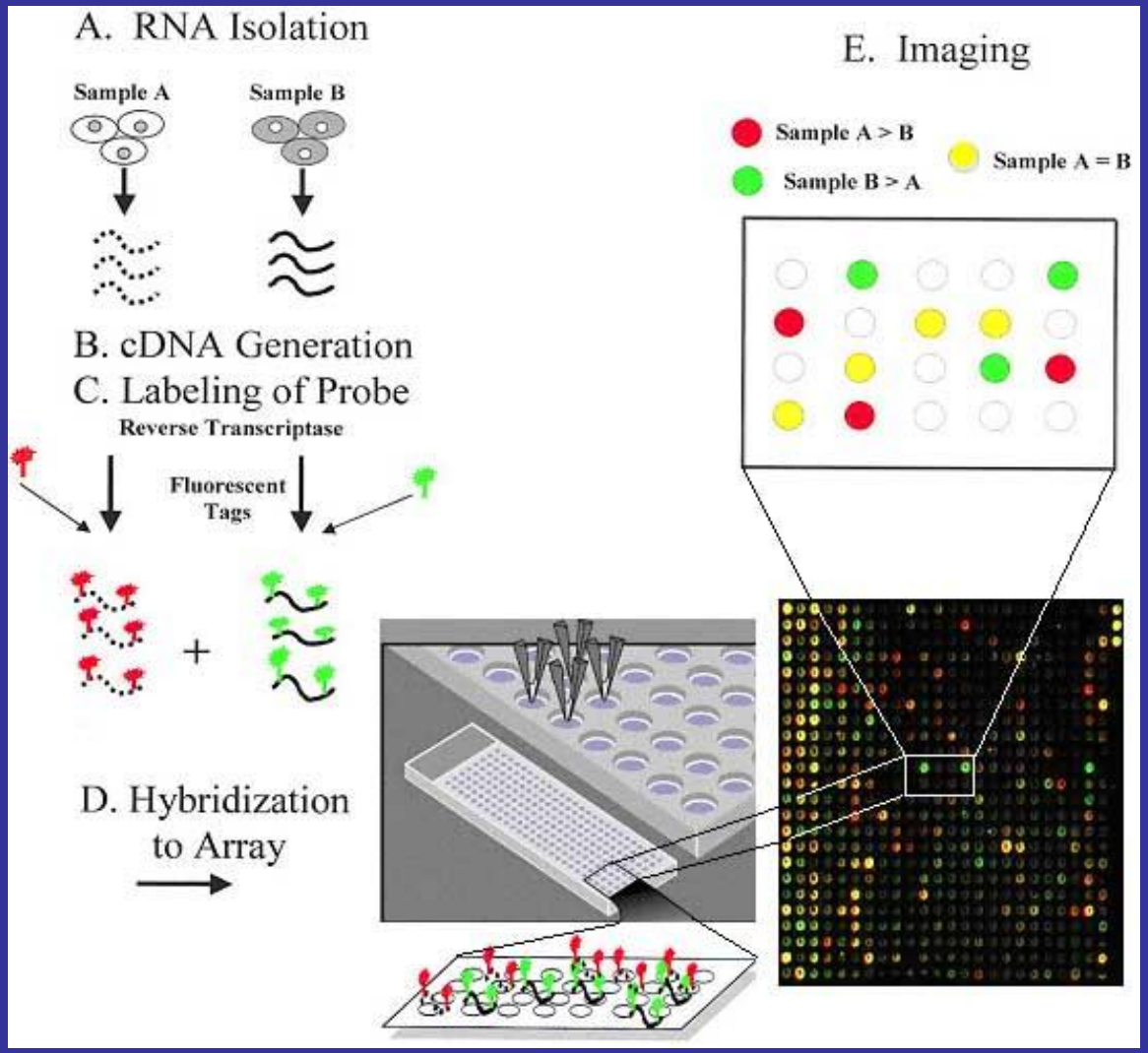


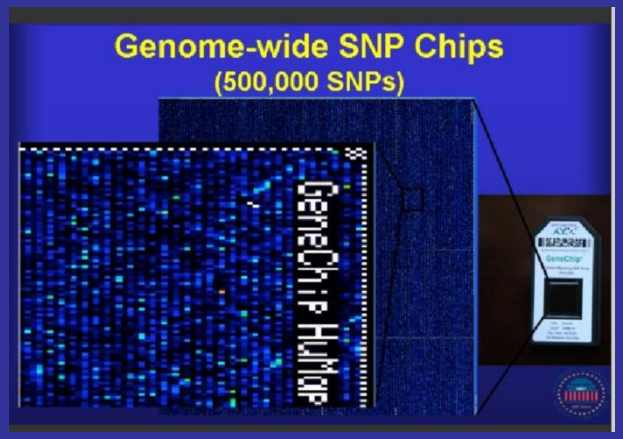
April 1953

April 2003

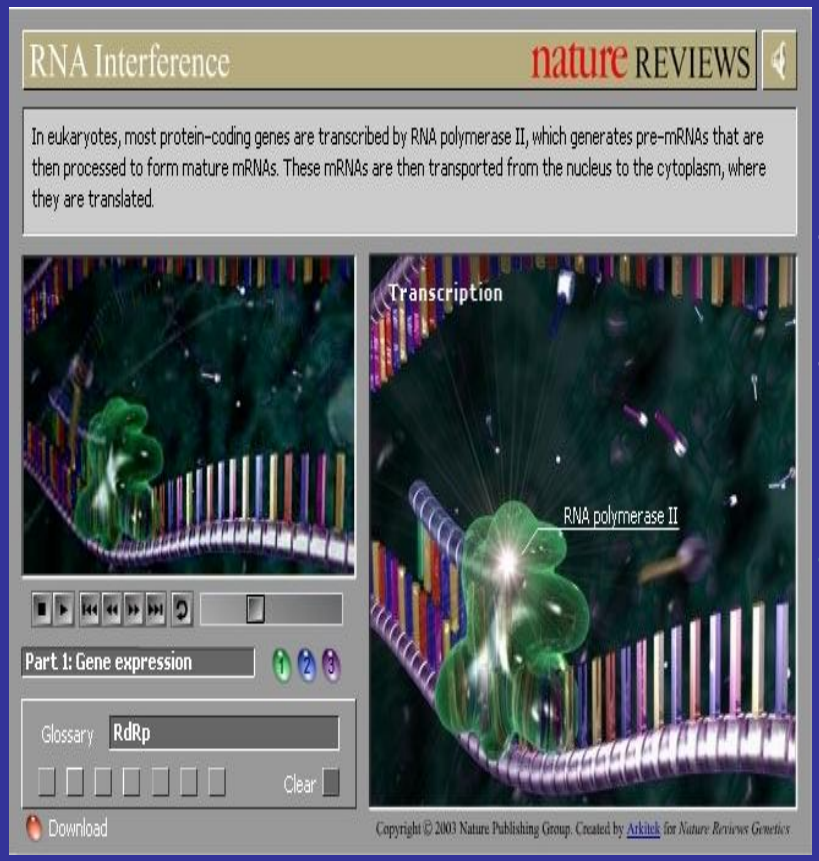


MICROARRAYS
GENE PROJECTS





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**

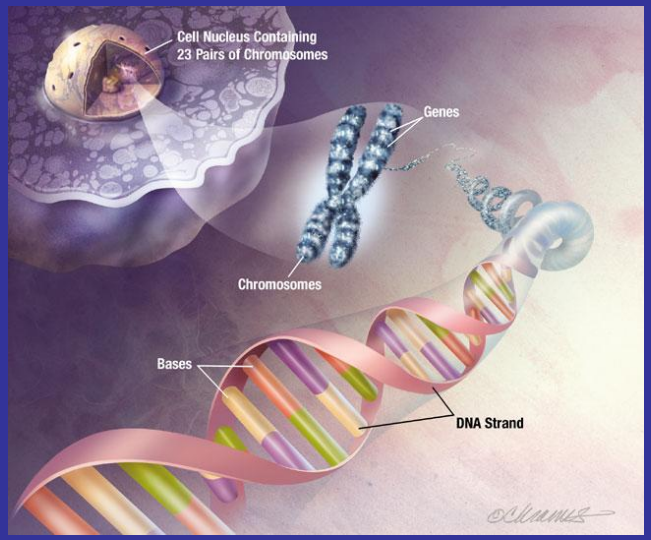
Sreekumar R, Halvatsiotis P, Nair S. Diabetes 51:1913-20, 2002

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

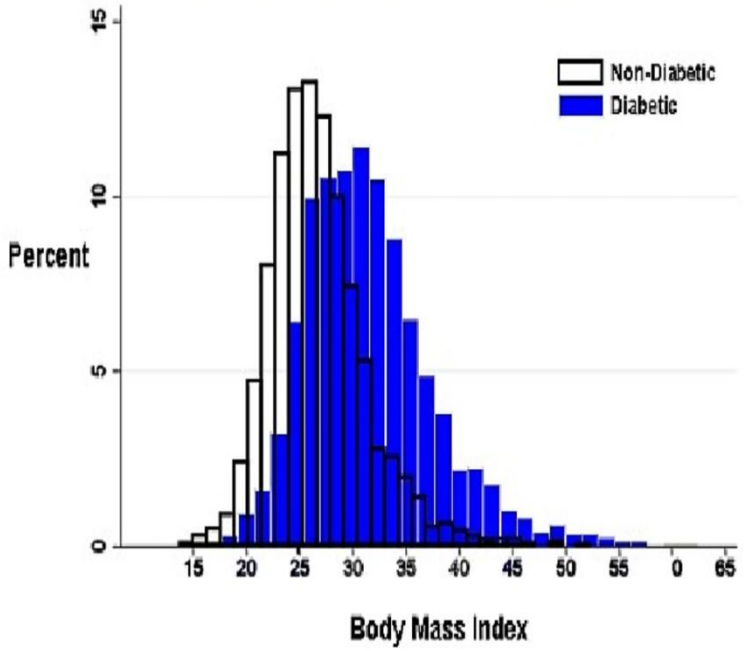
Gene Expression Profile in Skeletal Muscle of Type 2 Diabetes and the Effect of Insulin Treatment

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



GENOME WIDE ASSOCIATION STUDIES IN DIABETES MELLITUS

BMI is not the only determinant of Type 2 diabetes



DARTS study

2007 is a very good year for type 2 diabetes genetics!

Sciencexpress Report

April 26th 2007

Sciencexpress Report

April 26th 2007

Sciencexpress Report

Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels

April 26th 2007

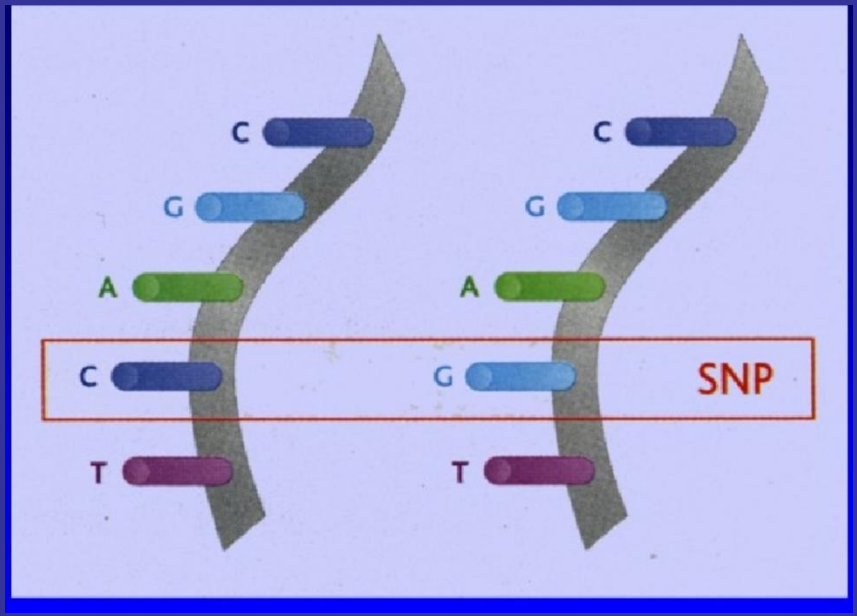
A variant in *CDKAL1* influences insulin response and risk of type 2 diabetes

April 26th 2007

Feb 11th 2007 ARTICLES

A genome-wide association study identifies novel risk loci for type 2 diabetes

SINGLE NUCLEOTIDE POLYMORPHISM



10.000.000 SNIPs

Polymorhism if present in <1%

Linkage studies

$p < 5 \times 10^{-7}$

But in practice,
only two are observed

...C...A...A...

...C...A...G...

...C...C...A...

...C...C...G...

...T...A...A...

...T...A...G...

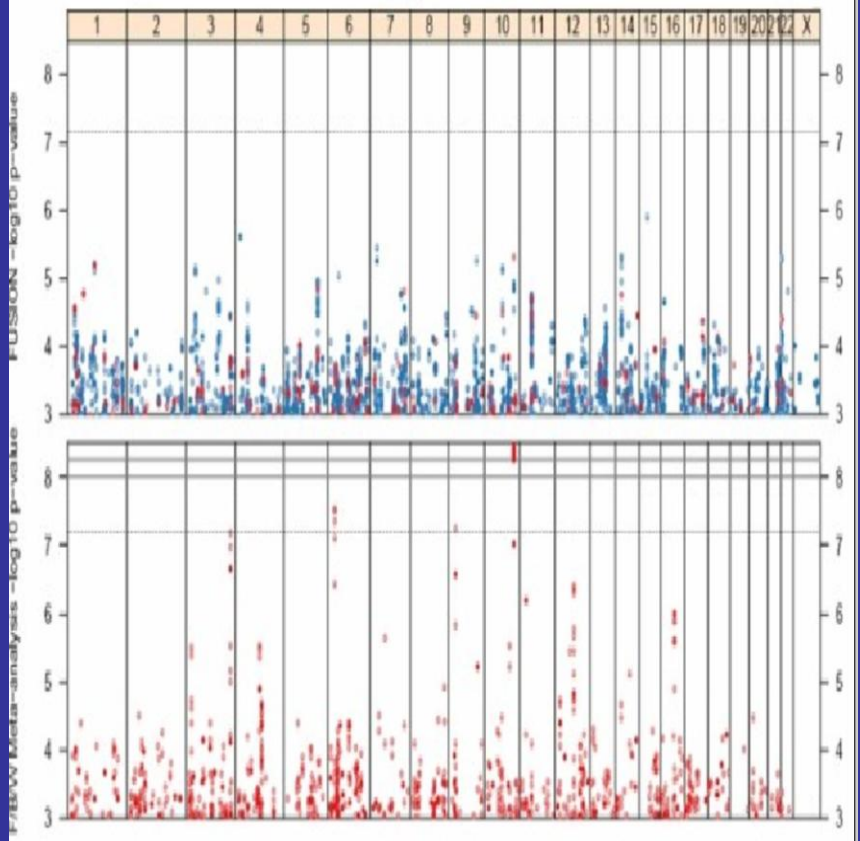
...T...C...A...

...T...C...G...

«DIABETOGENIC» GENES

Results of GWA with 317,503 SNPs

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



Stage 1 – FUSION + DGI + WTCCC

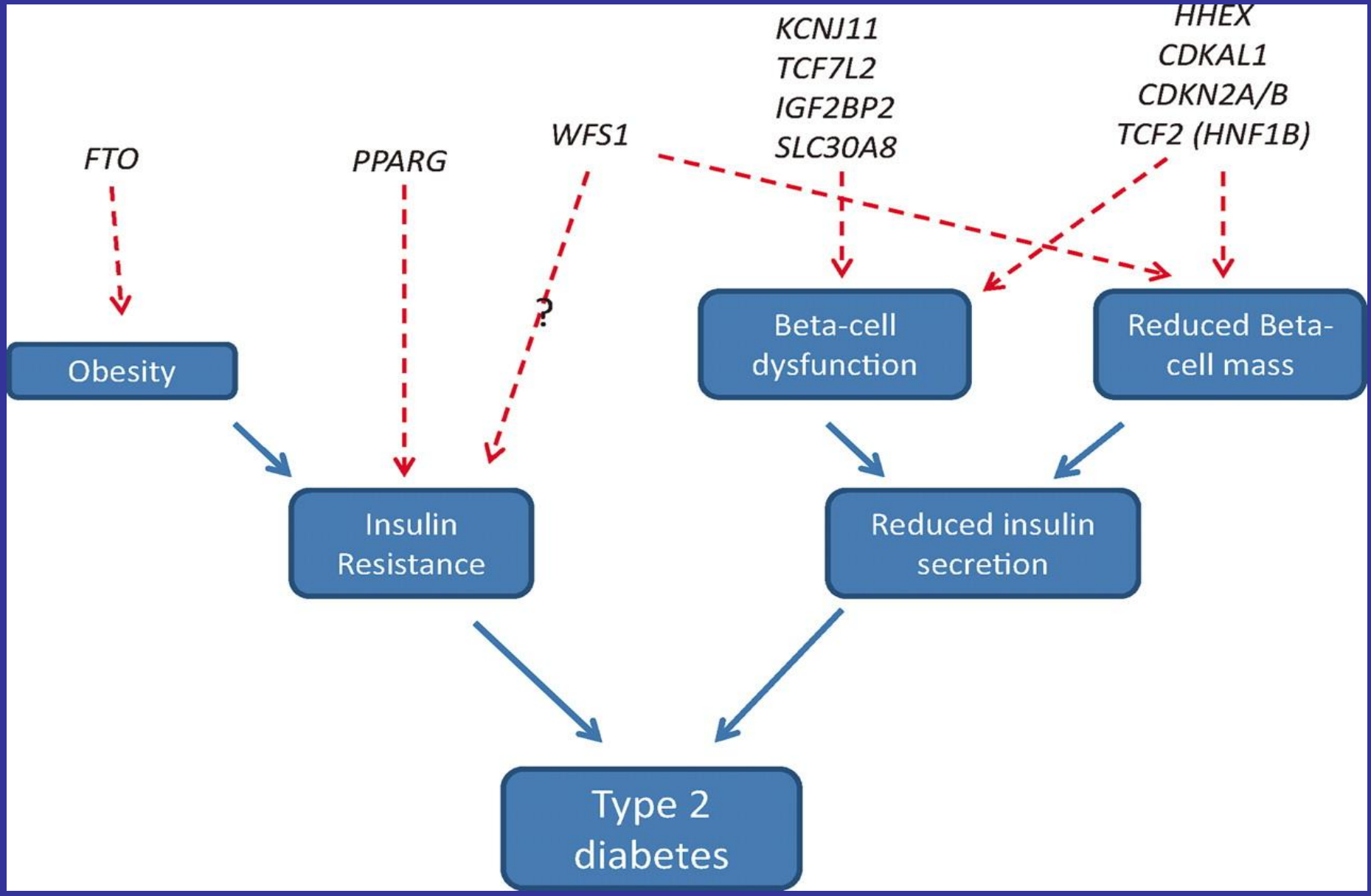
(4549 cases + 5579 controls)

Top 10 Results From Combined Analysis

n = 32,554

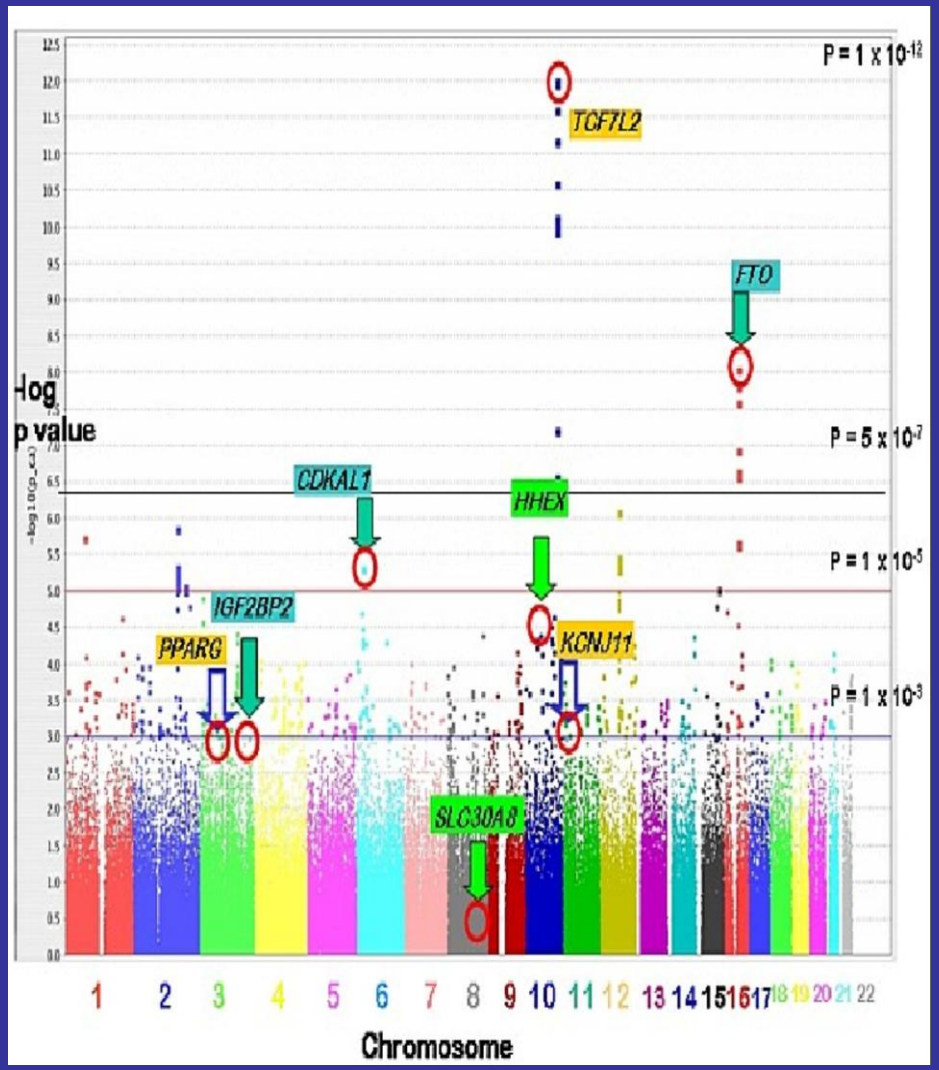
	FUSION		DGI		WTCCC/UKT2D		All Samples	
Gene	OR	p-value	OR	p-value	OR	p-value	OR	p-value
TCF7L2	1.34	1.3×10^{-8}	1.38	2.3×10^{-31}	1.37	6.7×10^{-13}	1.37	1.0×10^{-48}
IGF2BP2	1.18	2.1×10^{-4}	1.17	1.7×10^{-9}	1.11	1.6×10^{-4}	1.14	8.9×10^{-16}
CDKN2A/B	1.20	.0022	1.20	5.4×10^{-8}	1.19	4.9×10^{-7}	1.20	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}

DIABETES GENES

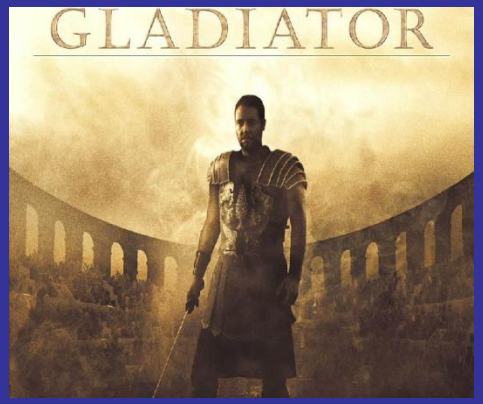


TCF7L2

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



Η ΔΙΑΙΤΑ ΤΟΥ ΜΟΝΟΜΑΧΟΥ

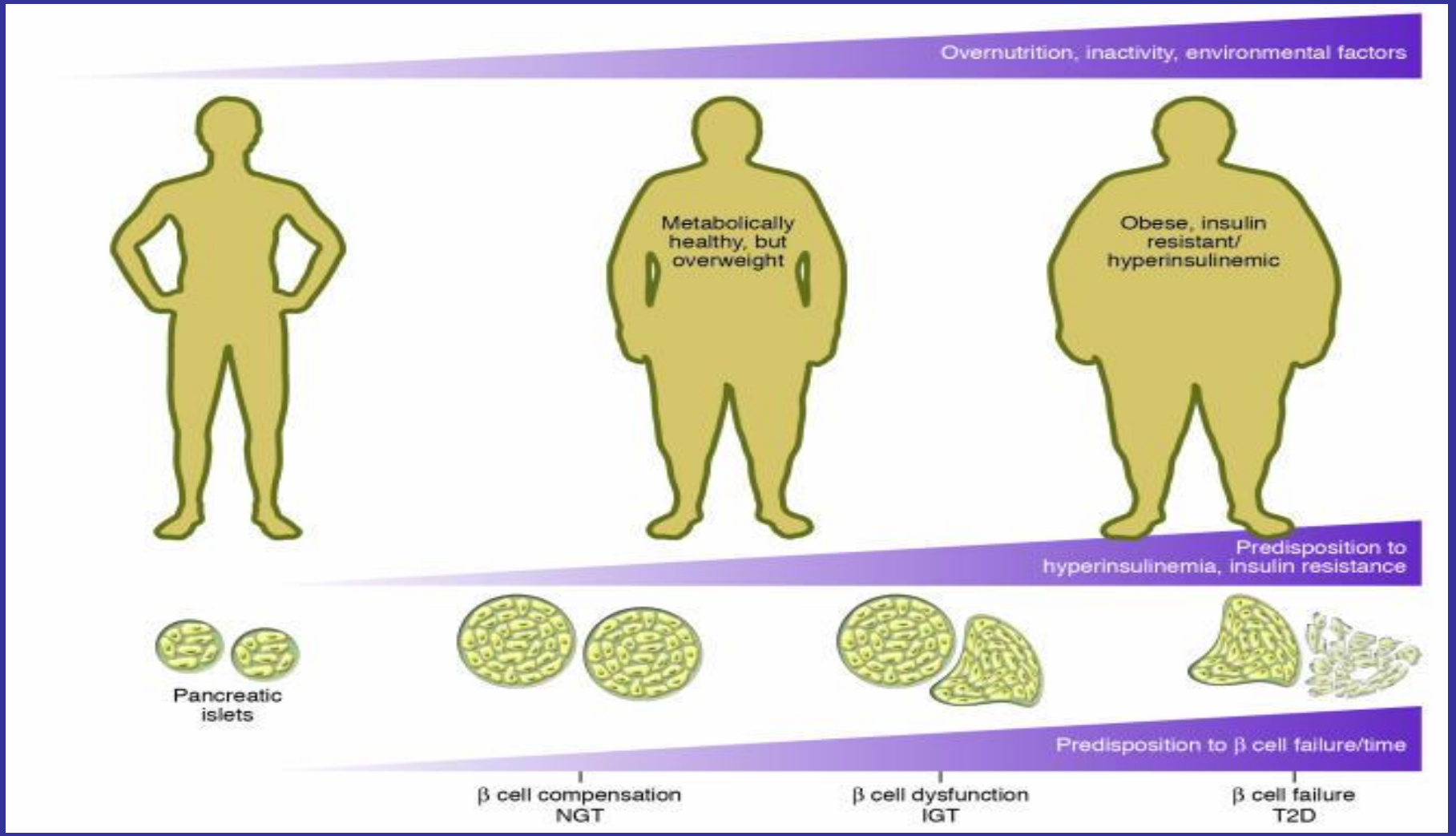


«Οι μονομάχοι ήταν απαραίτητο να διαθέτουν αρκετό υποδόριο λίπος, για να προστατεύονται από τους τραυματισμούς γιατί λειτουργεί ως «ασπίδα» για τα νεύρα και τα μεγάλα αγγεία. Επίσης τα τραύματα που αιμορραγούσαν ήταν πιο θεαματικά.»

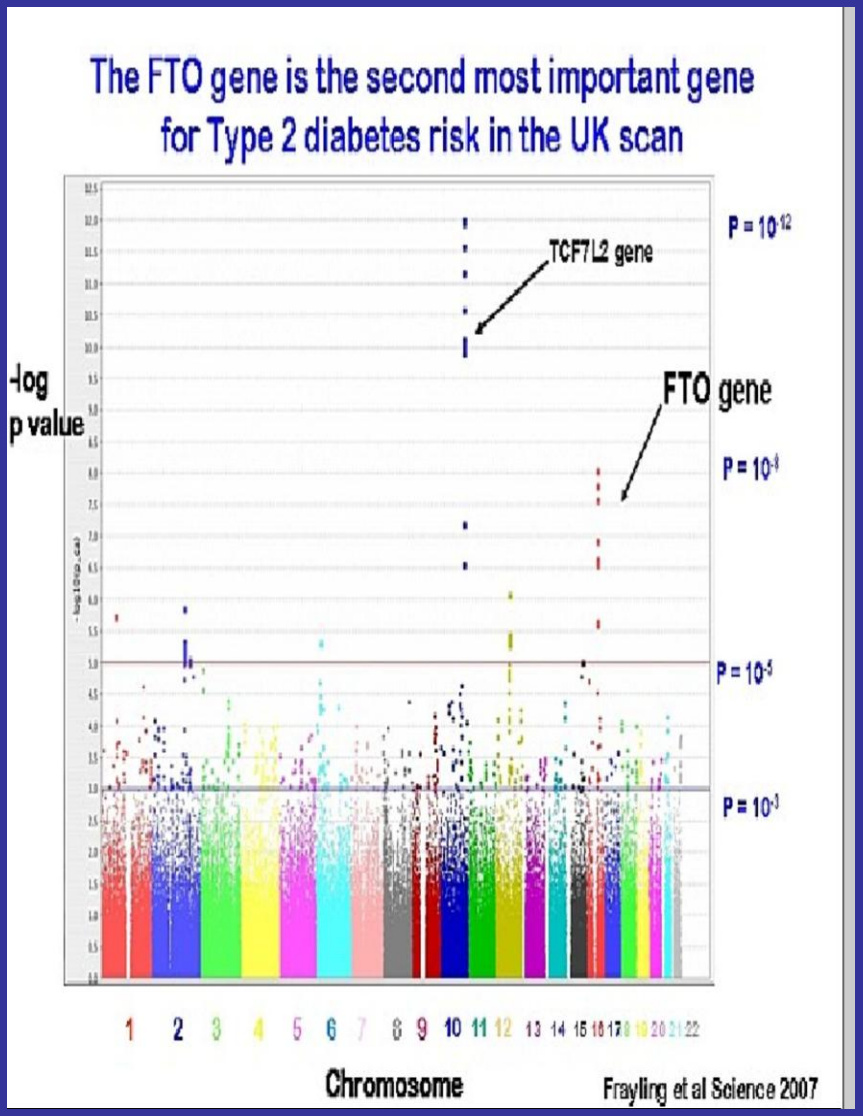
Karl Grossschmidt

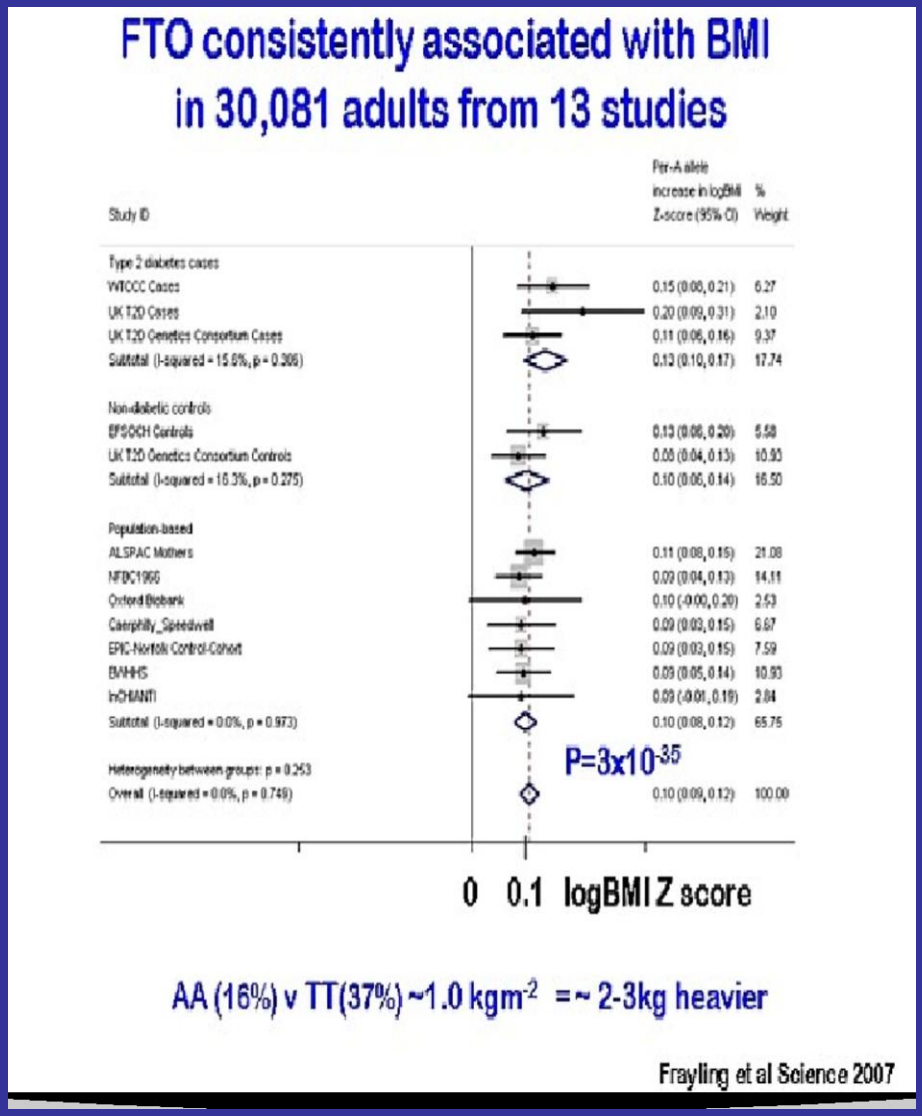
The London Times 12/15/02

β – ΚΥΤΤΑΡΟ & ΙΝΣΟΥΛΙΝΟΑΝΤΙΣΤΑΣΗ



FTO GENE


The FTO gene is the second most important gene for Type 2 diabetes risk in the UK scan
-log p value
TCF7L2 gene
FTO gene
P = 10-12
P = 10-6
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
Per-A allele increase in logBMI (Z-score (95% CI))
%
Study ID
Weight
Type 2 diabetes cases
WTCCC Cases 0.15 (0.09, 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
EPIGCH Controls 0.13 (0.06, 0.20) 5.58
UK T2D Genetics Consortium Controls 0.09 (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 (0.02, 0.15) 6.67
EPIC-Norfolk Control-Cohort 0.09 (0.02, 0.15) 7.59
BAMHS 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†]

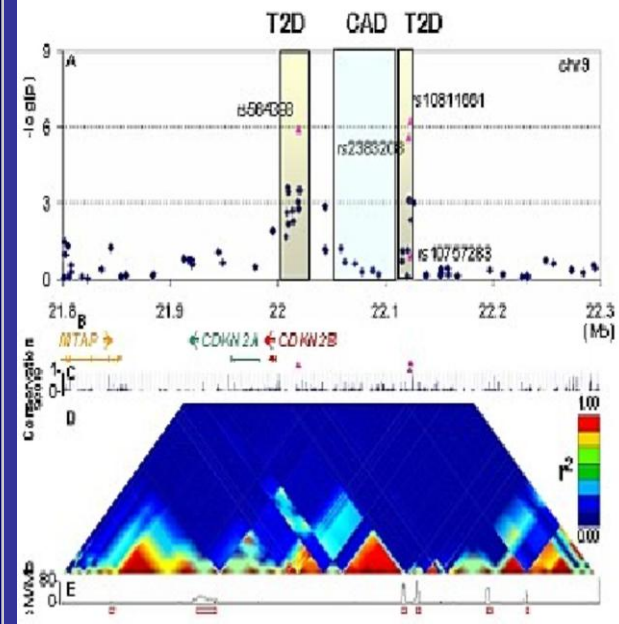
[1]Division of Cardiology, University of Ottawa Heart Institute, Ottawa K1Y4W7, Canada. [2]Donald W. Reynolds Cardiovascular Clinical Research Center and the Eugene McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. [3]Perlegen Sciences, Mountain View, CA 94043, USA. [4]Genomics Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA & U.S. Department of Energy Joint Genome Institute, Walnut Creek, CA 94598, USA. [5]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Copenhagen DK-2100, Denmark. [6]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN 55454, USA. [7]Human Genetics Center and Institute for Molecular Medicine, University of Texas Health

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,[3] 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 (1.06-1.28)	1.7×10^{-3}
DGI	1.20 (1.12-1.28)	5.4×10^{-8}
FUSION	1.20 (1.07-1.36)	2.2×10^{-6}
All	1.20 (1.14-1.25)	7.8×10^{-15}

	OR	p
WTCCC	1.15 (1.07-1.27)	3.2×10^{-4}
UK rep	1.12 (1.05-1.19)	6.6×10^{-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}

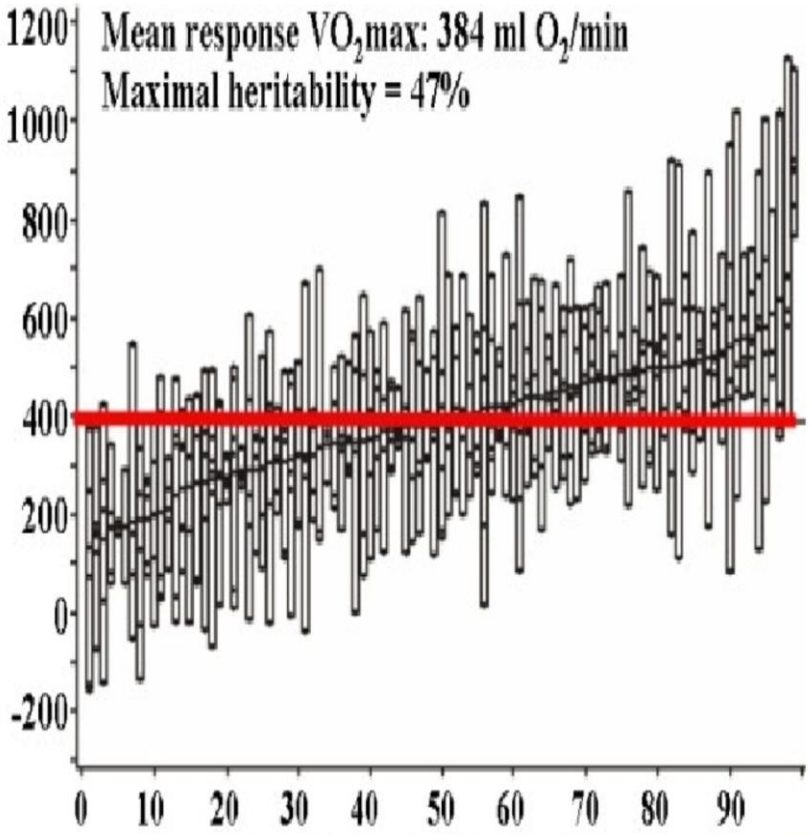
Zeggini et al Science 2007 & WTCCC Nature 2007

ΑΠΟΔΟΣΗ ΣΤΗΝ ΑΣΚΗΣΗ

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

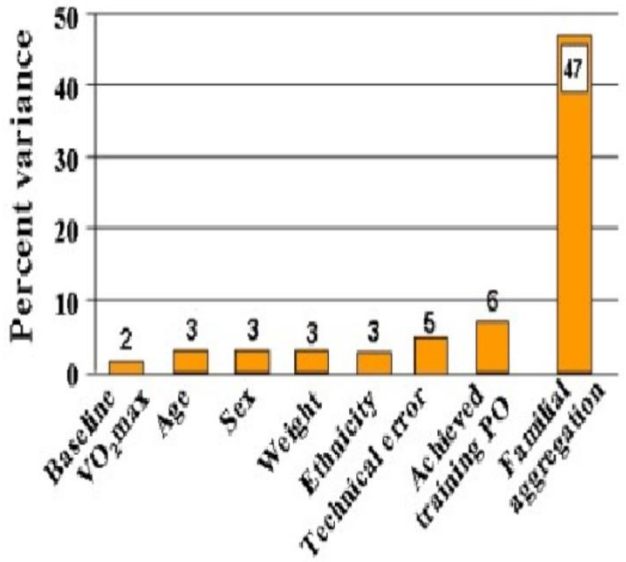
VO_2max Response in Whites of HFS



Bouchard et al, JAP, 1999

HERITAGE FAMILY STUDY

VO_2max Training Response in HFS



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

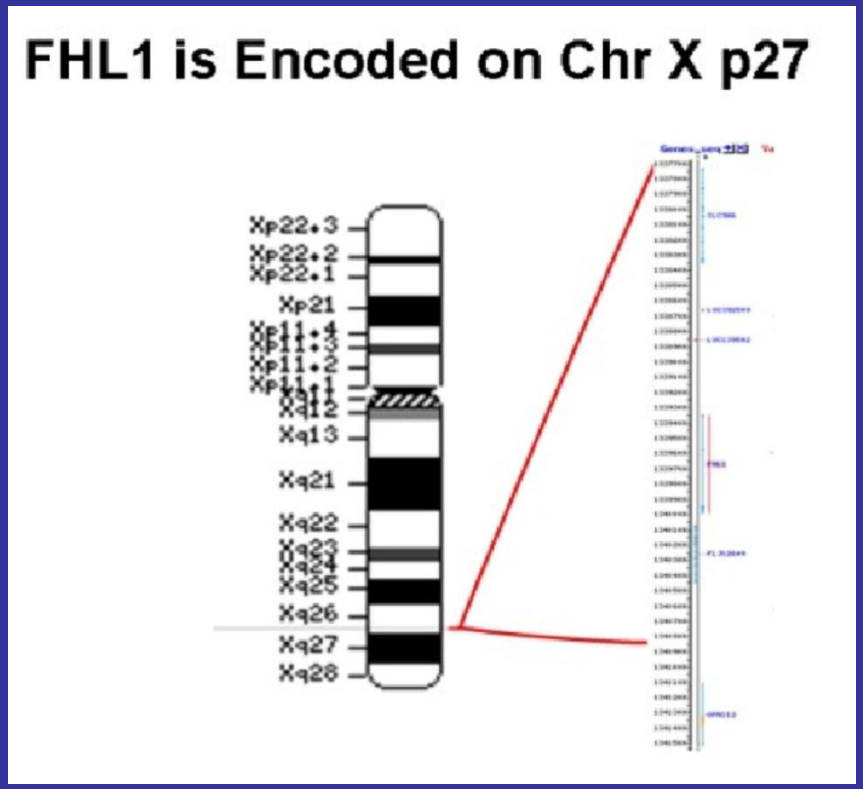
Bouchard et al, JAP, 1999

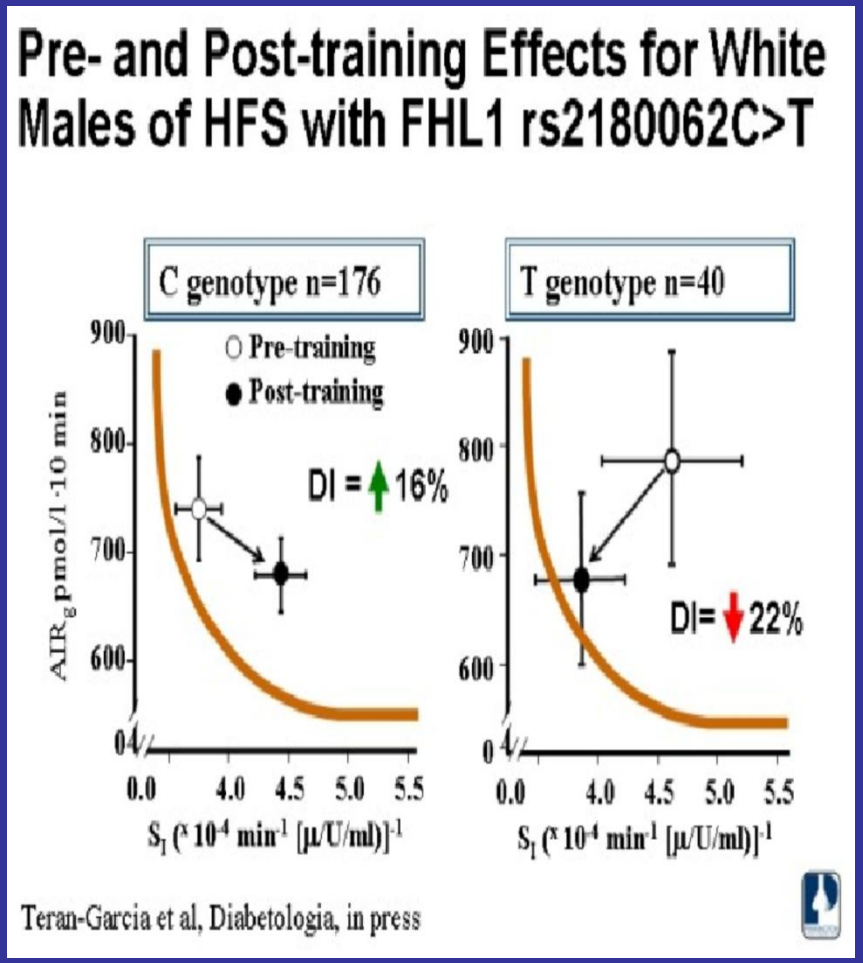
ΓΟΝΙΔΙΑ «ΚΛΕΙΔΙΑ» ΓΙΑ ΚΑΛΥΤΕΡΗ ΑΠΟΔΟΣΗ ΣΤΗΝ ΑΣΚΗΣΗ

Single Gene Defects Affecting the Adaptation to Exercise

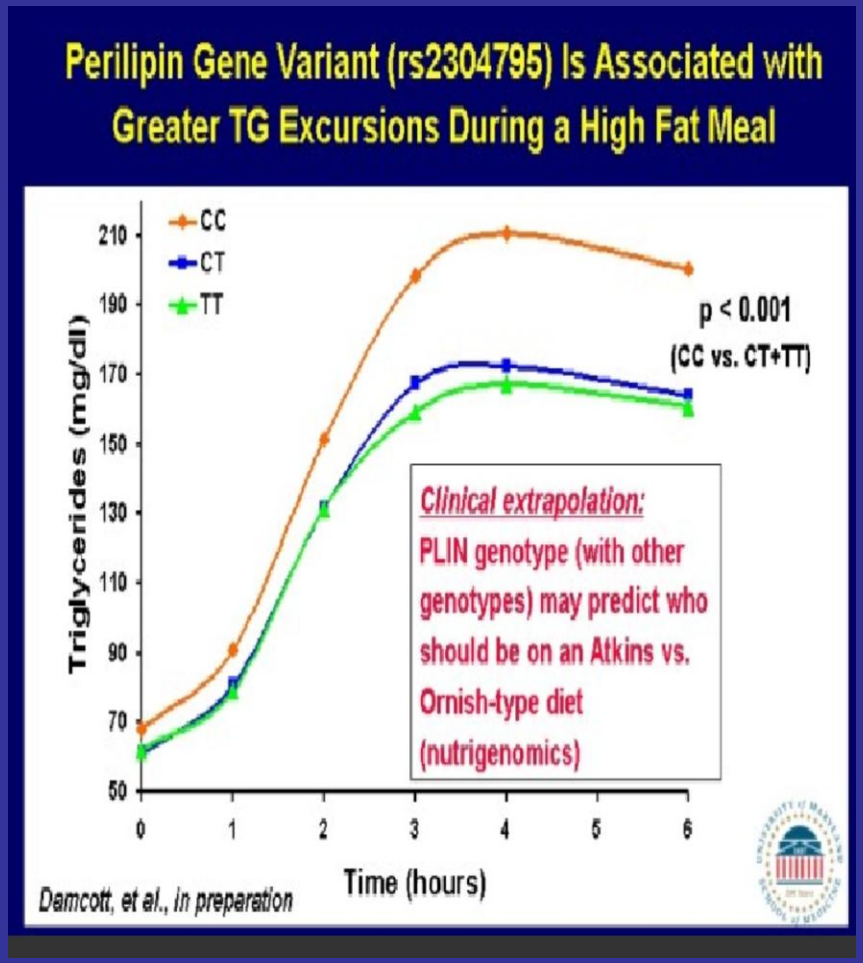
- Genes affecting cardiac performance
- Genes affecting oxygen transport
- Genes affecting skeletal muscle glycogen metabolism
- Genes affecting skeletal muscle lipid metabolism
- Genes affecting mitochondrial biology

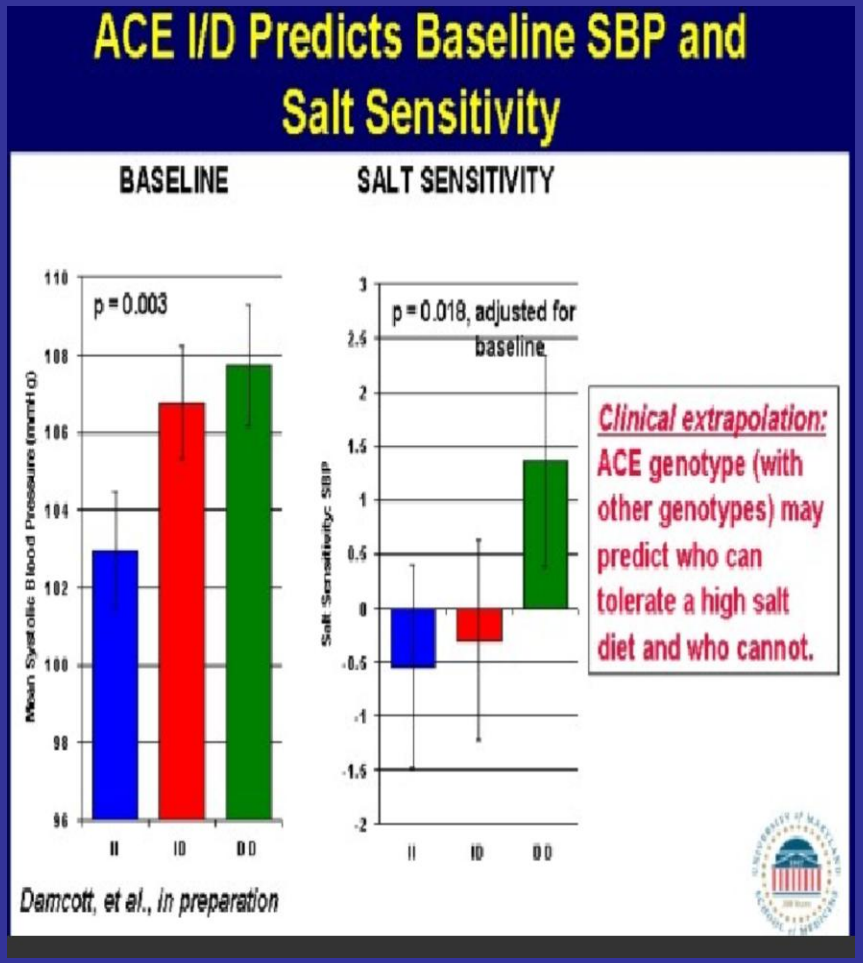
ΑΣΚΗΣΗ - ΓΟΝΙΔΙΑΚΟ ΥΠΟΣΤΡΩΜΑ & ΙΝΣΟΥΛΙΝΙΚΗ ΕΥΑΙΣΘΗΣΙΑ



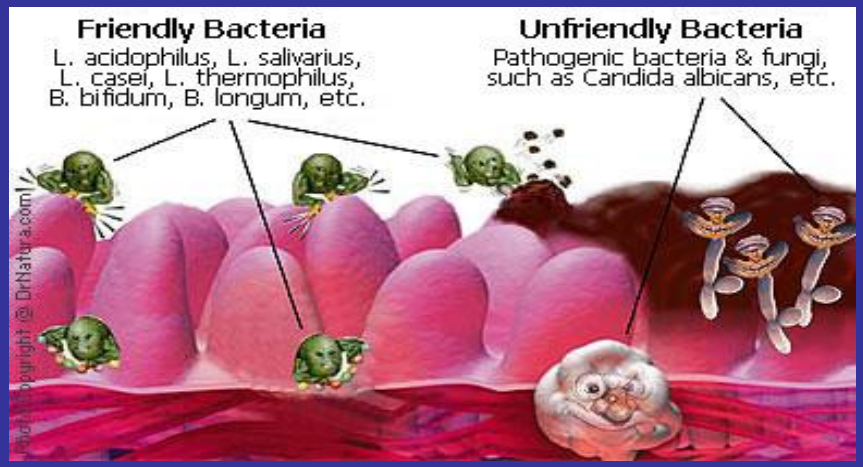


ΜΕΤΑΒΟΛΙΚΕΣ ΠΑΡΑΜΕΤΡΟΙ & ΑΠΛΟΤΥΠΟΙ



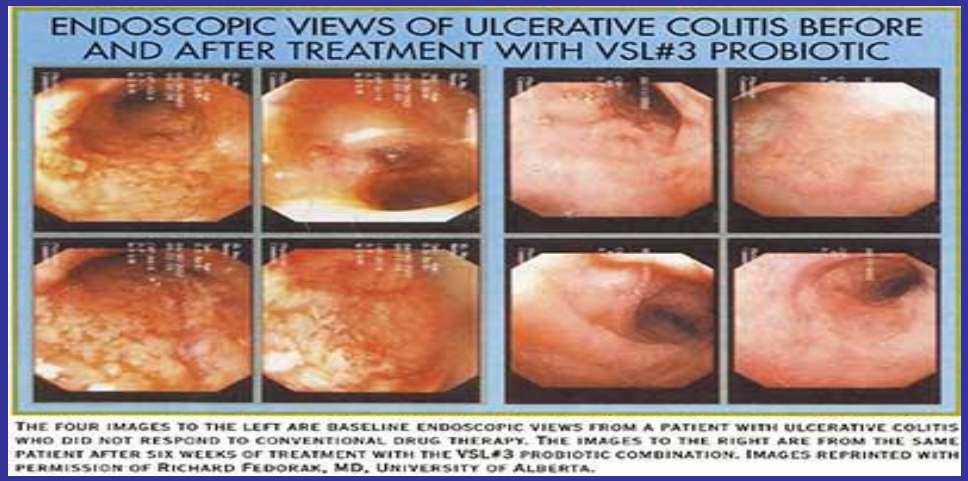


BACTERIA & HEALTH

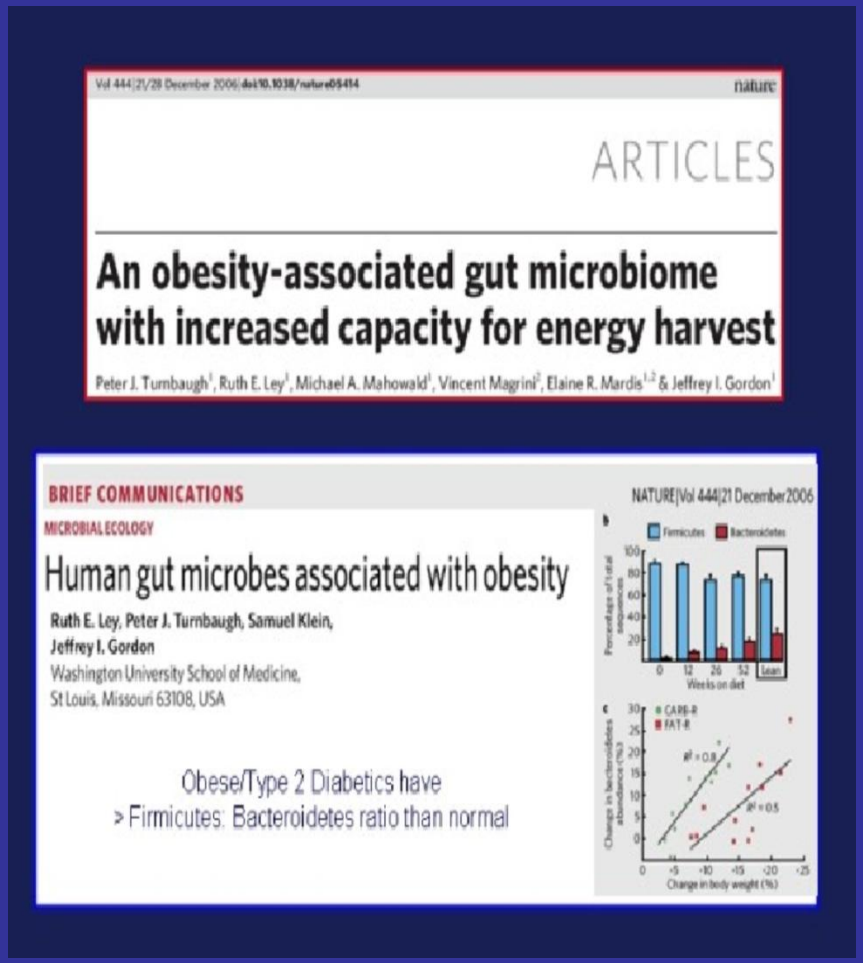


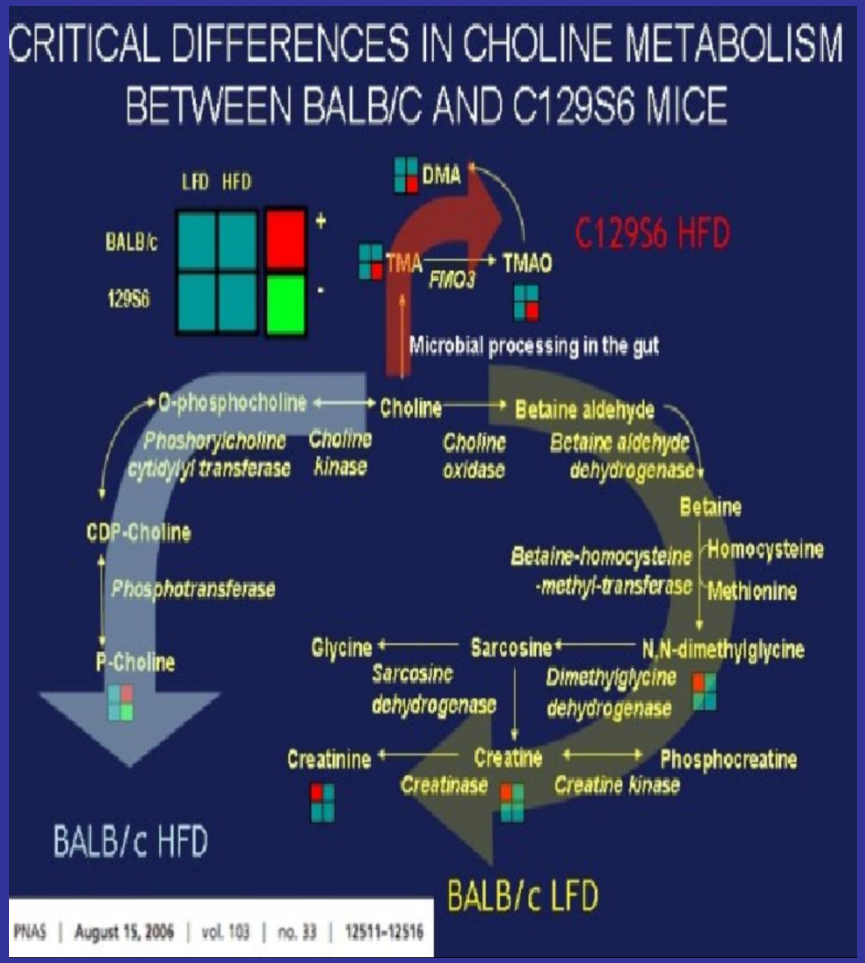
YOGURT & PROBIOTICS

PERIODONTITIS & MI

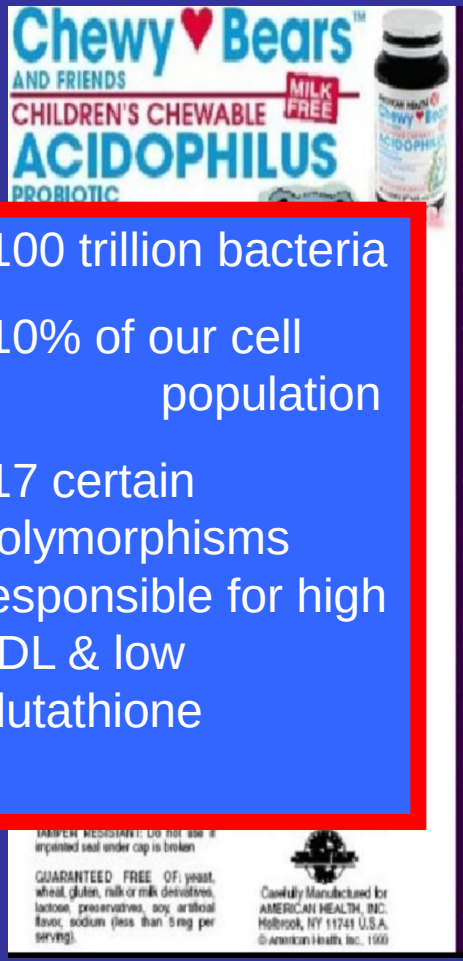


HOW HUMANS WE ARE?





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?

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

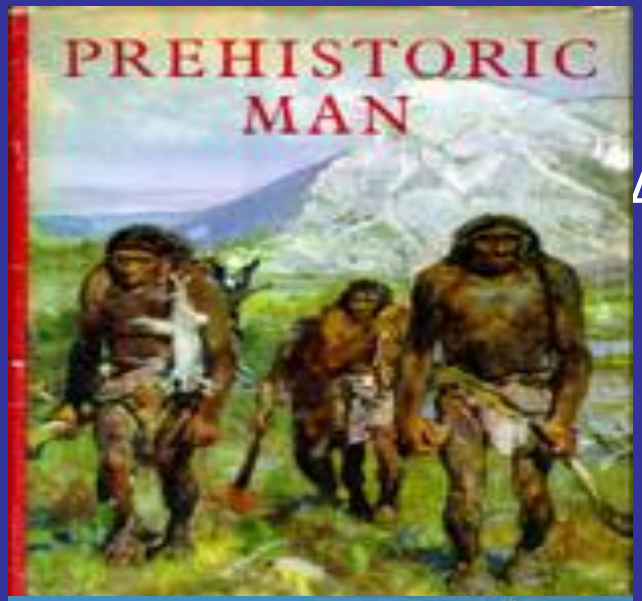
asthma, eczema, psoriasis....

Insulin resistance related diseases- type 2 diabetes and obesity...

Many neuropsychiatric disorders....

“THRIFTY GENOTYPE”

ΔΙΑΤΡΟΦΗ & ΜΕΤΑΒΟΛΙΚΟ ΣΥΝΔΡΟΜΟ



Διατροφή: πλούσια σε πρωτεΐνες,
πτωχή σε υδατάνθρακες
χαμηλά επίπεδα ινσουλίνης

→ Αυξημένη φυσική δραστηριότητα

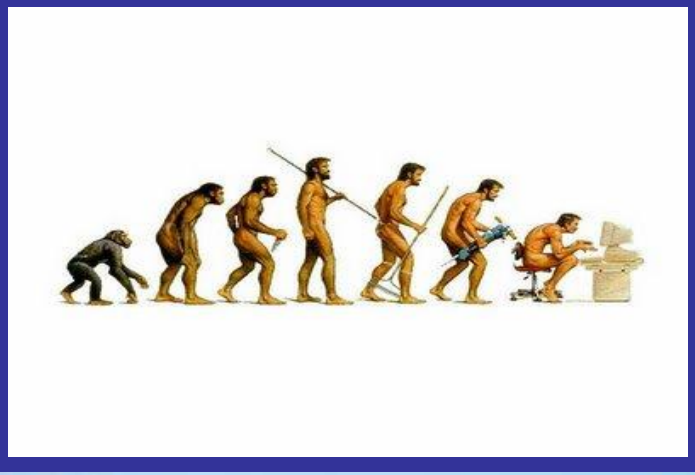
"Thrifty genes"

Διατροφή: τρόφιμα υψηλού γλυκαιμικού δείκτη & πλούσια σε λιπαρά

→ μεταγευματική υπερινσουλιναιμία
παχυσαρκία ,
μεταβολικό σύνδρομο & Σ.Διαβήτη

Εποχή του τηλε - control

ΛΟΓΟΙ ΜΕΙΩΜΕΝΗΣ ΦΥΣΙΚΗΣ ΔΡΑΣΤΗΡΙΟΤΗΤΑ



ΠΡΙΝ ΤΗΝ ΕΚΒΙΟΜΗΧΑΝΙΣΗ

Υπαίθρια παιγνίδια, κυνήγι,
αγροτικές ασχολίες, Κατασκευές
Περπάτημα-μεταφορές
Τρόφιμα δυσεύρετα

ΜΕΤΑ ΤΗΝ ΕΚΒΙΟΜΗΧΑΝΙΣΗ

Τηλεκοντρόλ, κεντρική θέρμανση
Αυτοκίνητα, μηχανές,
internet shopping

THRIFTY GENOTYPE

Animal models of the thrifty genotype








Egyptian sand rat
(*Psammomys obesus*)

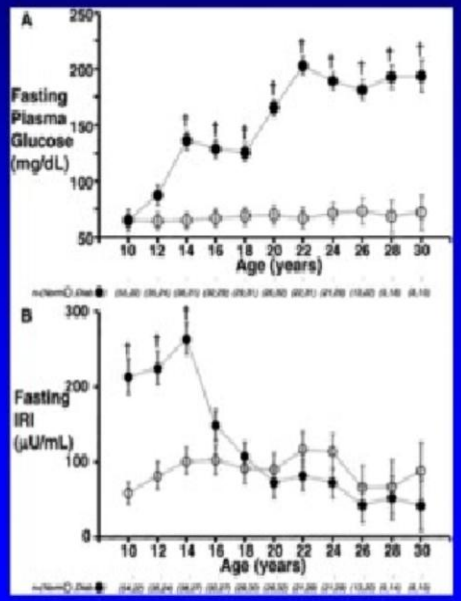
Spiny mouse
(*Acomys cahirinus*)

Tuco-tuco
(*Ctenomys talarum*)

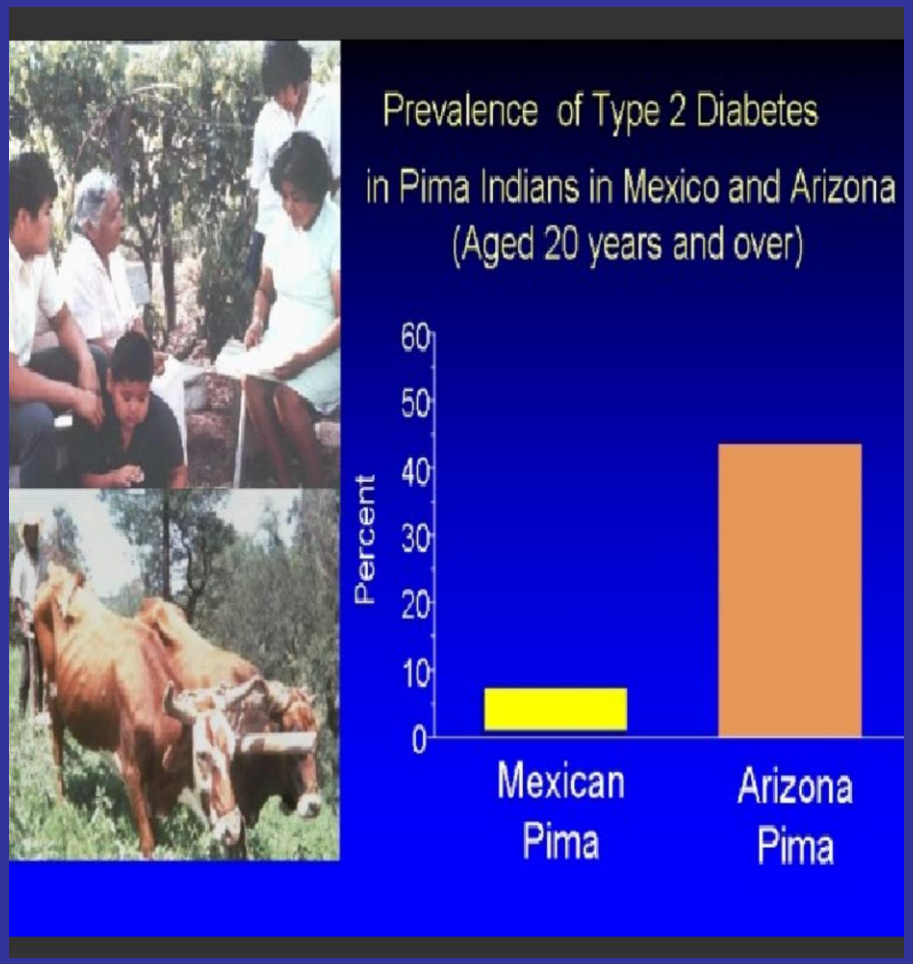
Round-tailed Ground Squirrel
(*Spermophilus tereticaudus*)

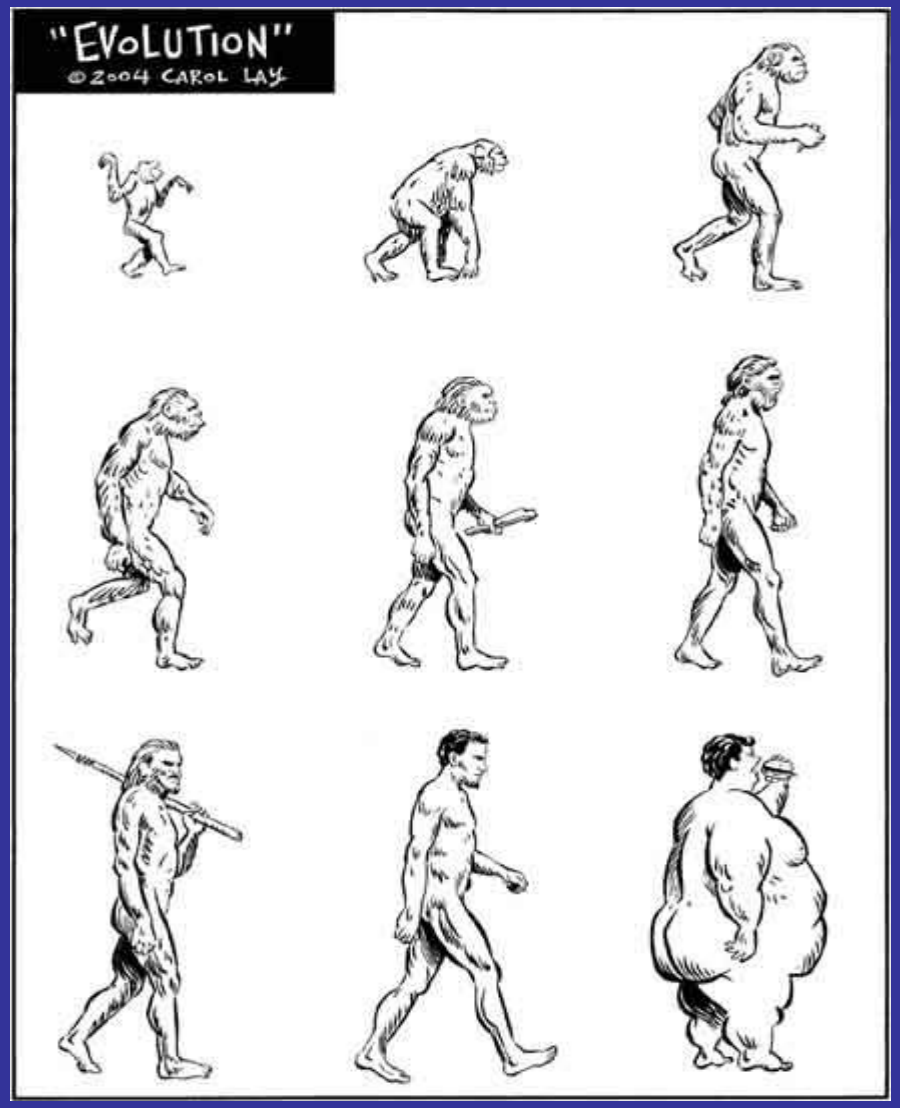
Animal models of the thrifty genotype


Rhesus macaque
(*Macaca mulatta*)

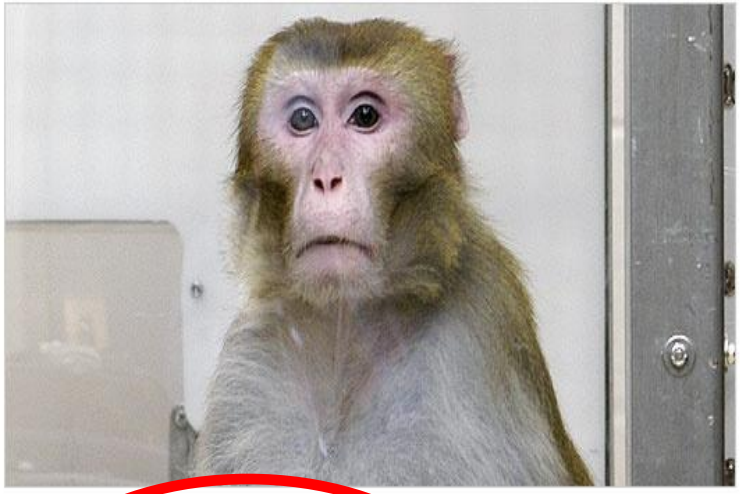


PIMA INDIANS





CALORIC RESTRICTION & AGING



CALORIE RESTRICTION DIET

Canto, 25

Although a senior citizen — the average rhesus monkey lifespan in captivity is 27 — Canto, above, is aging fairly well. Outwardly, he has a nice coat, elastic skin, a smooth gait, upright posture and an energetic demeanor. His bloodwork shows he is as healthy as he looks.

Human equivalent Meals prepared by Mike Linksvayer, 36

NORMAL DIET

Owen, 26

He gets more food, but Owen, above, isn't aging as well. His posture has been affected by arthritis. His skin is wrinkled and his hair is falling out. Owen is frail and moves slowly. His bloodwork shows unhealthy levels of glucose and triglycerides.

Diet of an average, active human male of 36

MONKEY MENU

Daily calories

445 885

Monkeys also receive an apple each day.

HUMAN MENU

Daily calories

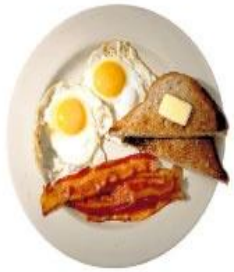
2,000 3,000

Beverages, snacks and desserts not shown. Diet varies according to body type, sex and activity level.

Breakfast fermented soybeans and garlic

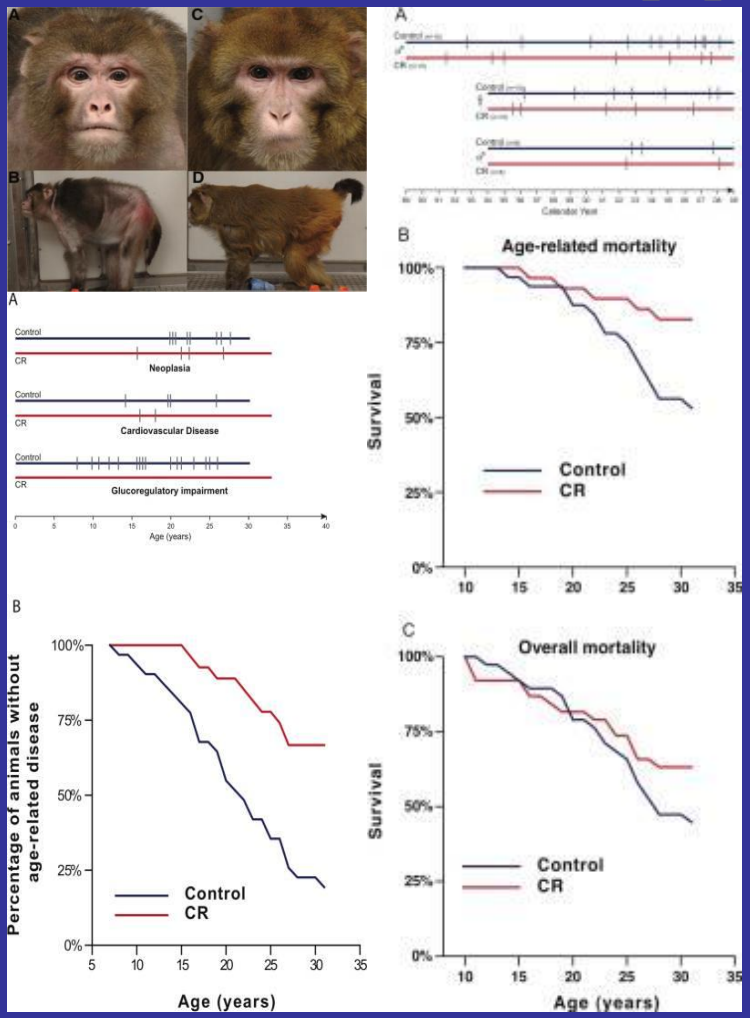
Lunch tofu, konyakku and carrots

Dinner vegan sausage, kale, tomato sauce and salad



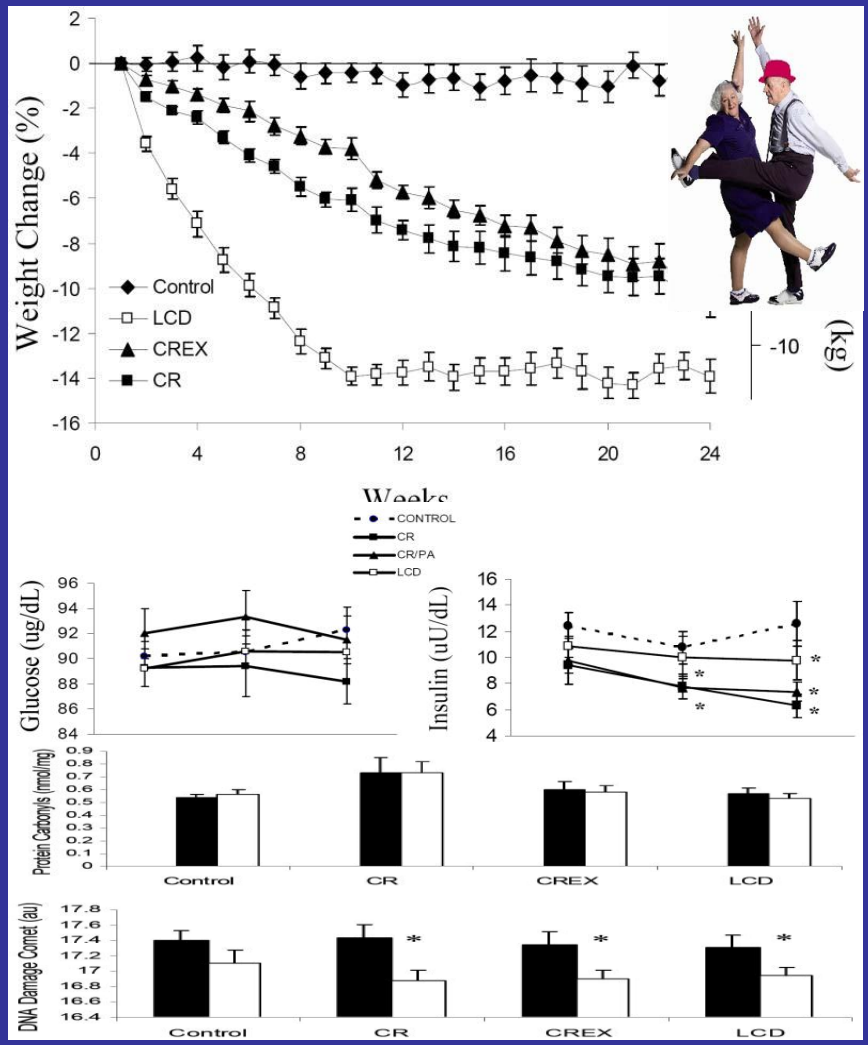
Photos by Jim Wilson and Tony Cenicola/The New York Times and Lars Klove for The New York Times

CALORIC RESTRICTION & AGING



RJ Colman & R Weindruch

Science. 2009; 325(5937): 201–4

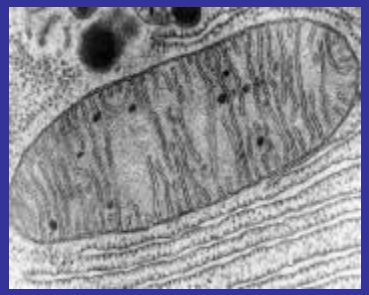


LK Heilbronn et al JAMA. 2006; 295(13):1539–48

Ο τελικός προορισμός της τροφής είναι η «καύση» στα μιτοχόνδρια

15 000kg during life

O_2



CO2
H2O
ATP
θερμότητα

~100 kg
Λίπος, γλυκογόνο, πρωτεΐνες

Η «ΔΕΗ» ΤΟΥ ΚΥΤΤΑΡΟΥ

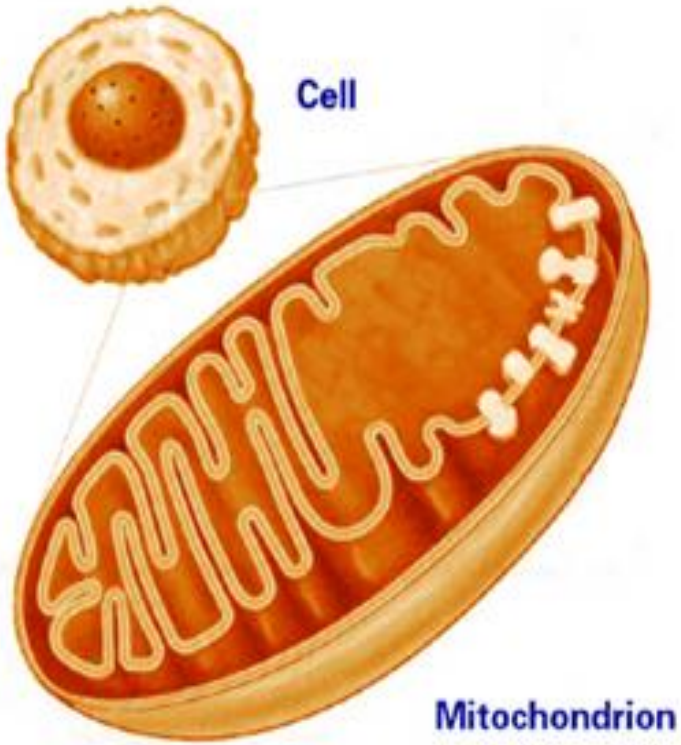


Fig. 1. A mitochondrion, one of the "intracellular powerhouses" found in every cell of the body.

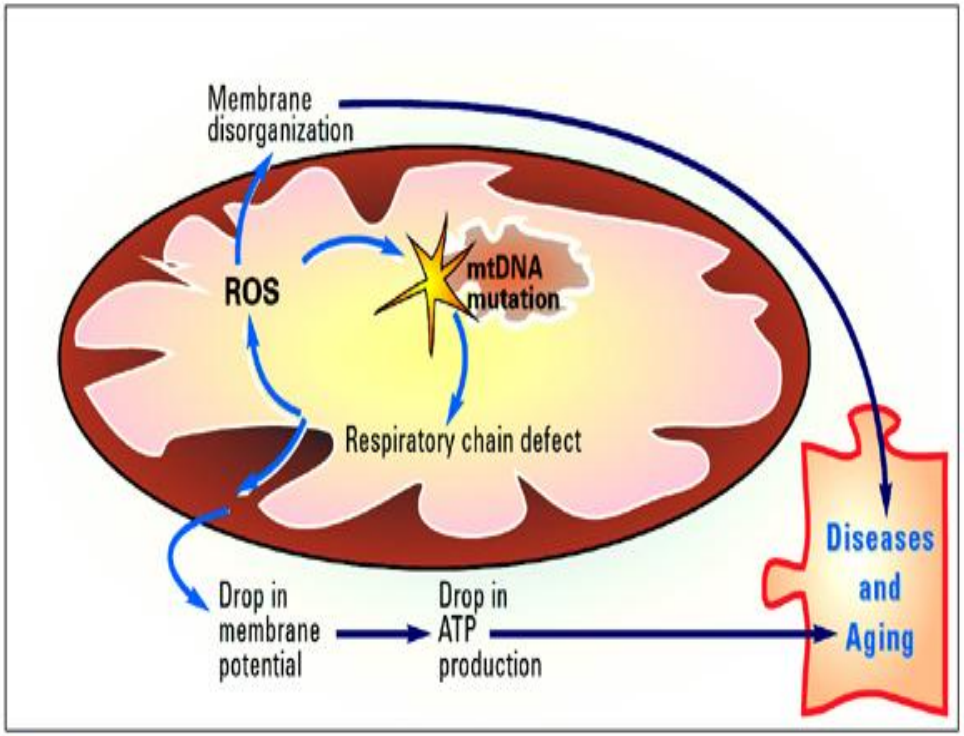
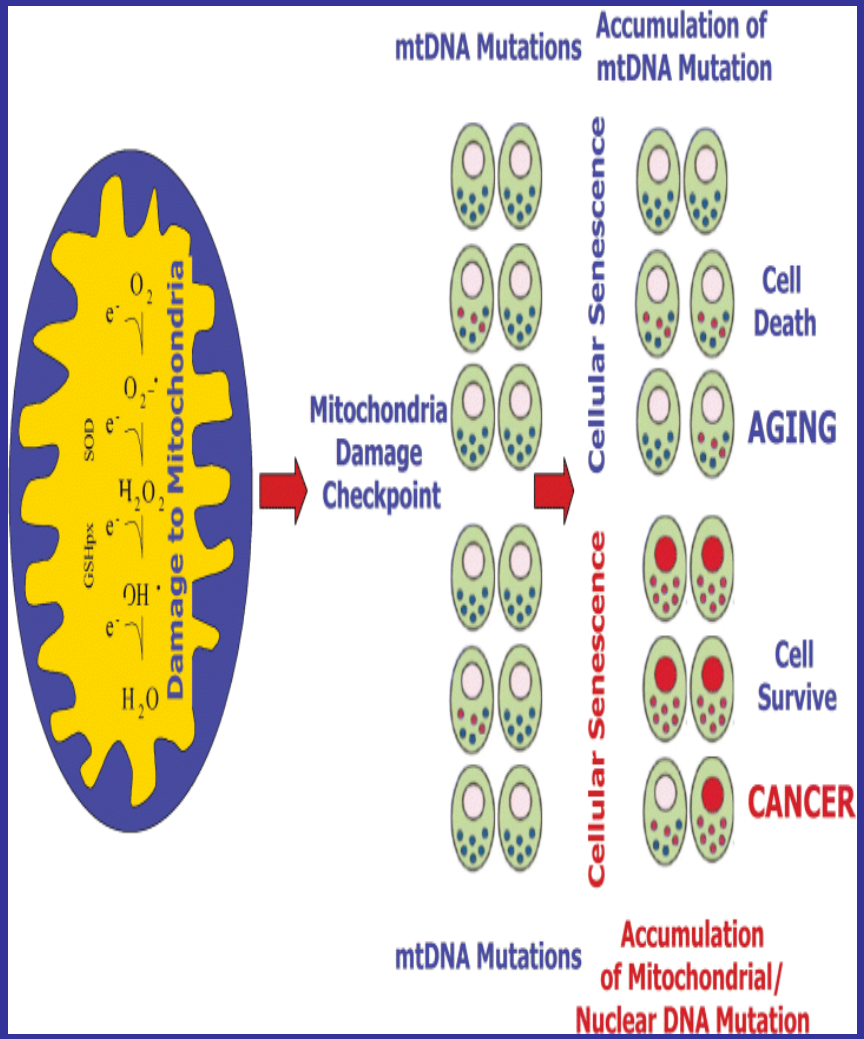


Fig. 6. Possible mechanisms of mitochondrial dysfunction include (1) Mitochondrial DNA (mtDNA) mutation caused by free radical damage; (2) Krebs' cycle decreased efficiency due to inadequate Krebs' cycle intermediates; (3) Respiratory chain defect due to enzyme and substrate alterations; and (4) Membrane disorganization and loss of fluidity. (Rustin, P. et al. "Defective mitochondria, free radicals, cell death—Reality or myth-ochondria," *Mech Age Develop*, 2000-206.)

ΟΞΕΙΔΩΤΙΚΟ STRESS ΜΙΤΟΧΟΝΔΡΙΩΝ



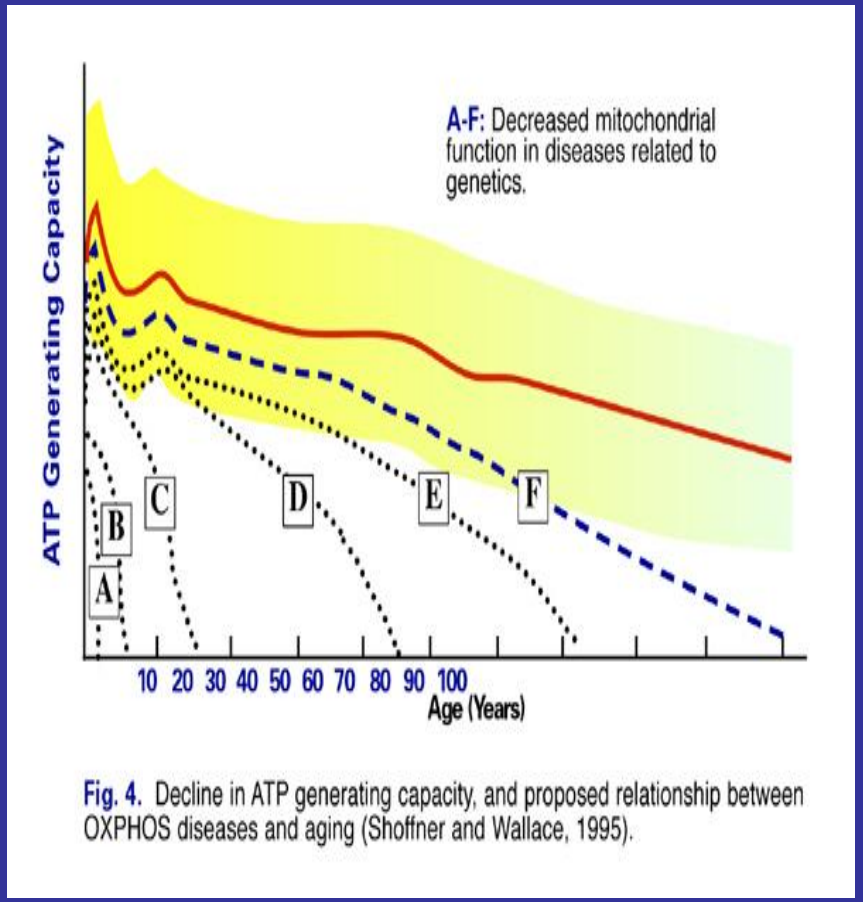
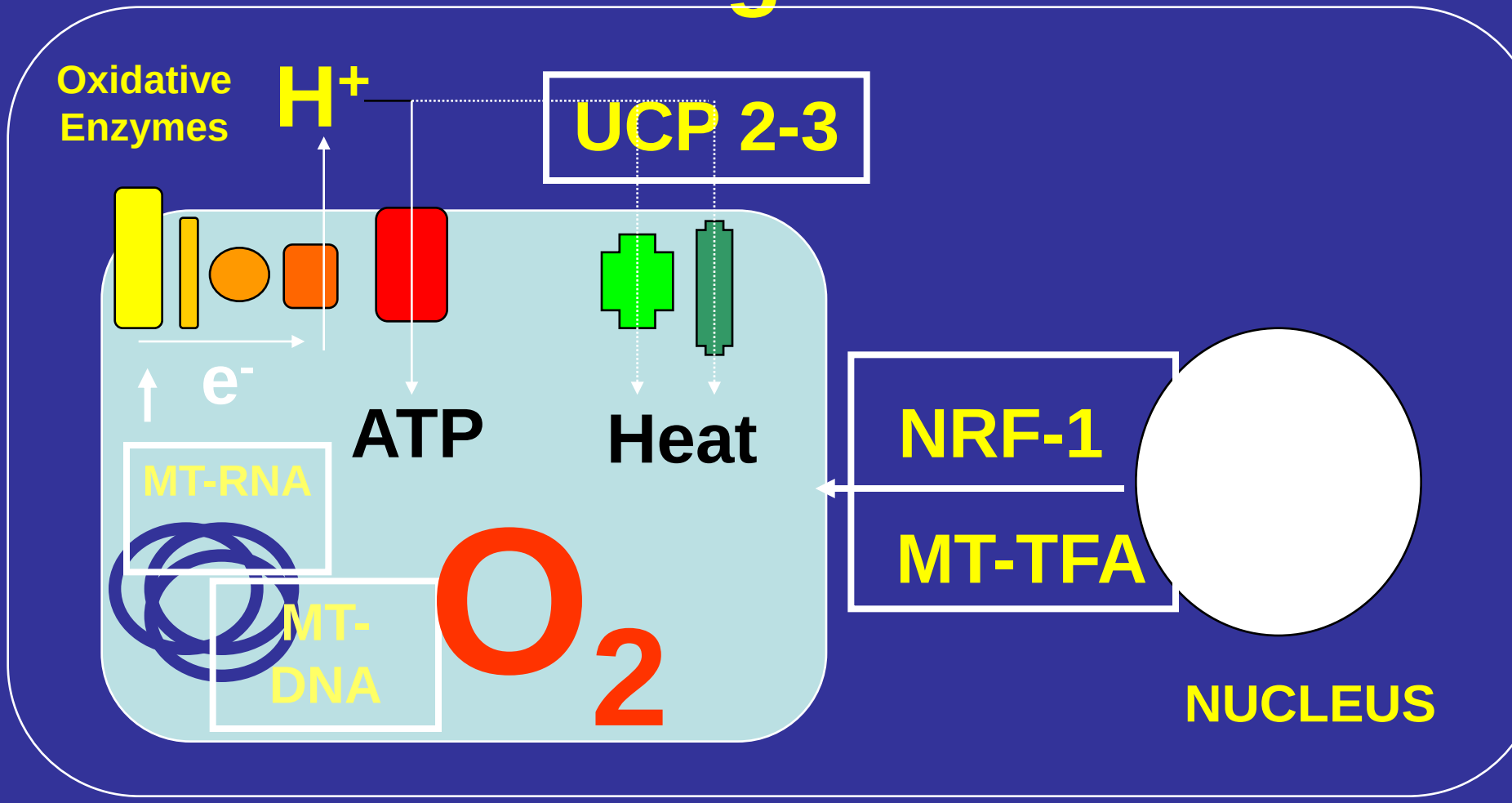


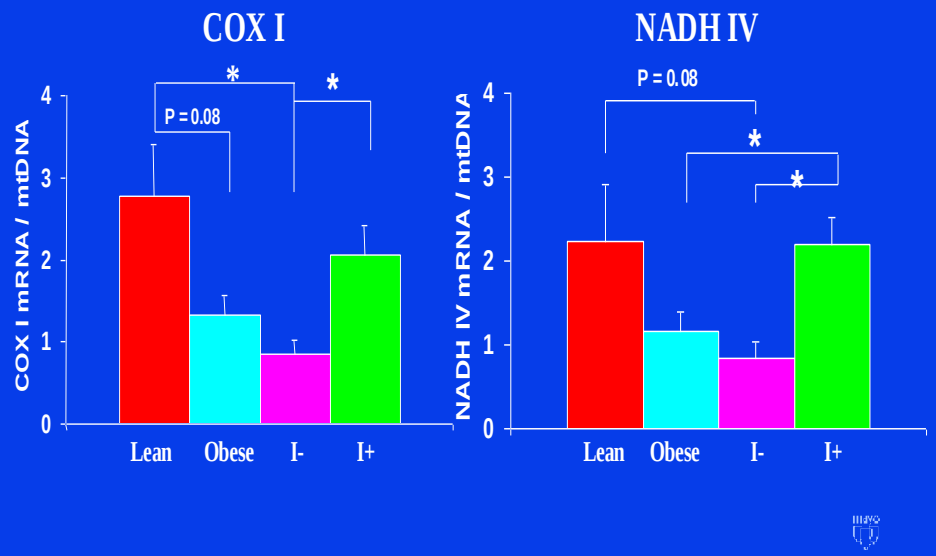
Fig. 4. Decline in ATP generating capacity, and proposed relationship between OXPHOS diseases and aging (Shoffner and Wallace, 1995).

Mitochondrial Oxidative Metabolism Potential Regulation Sites

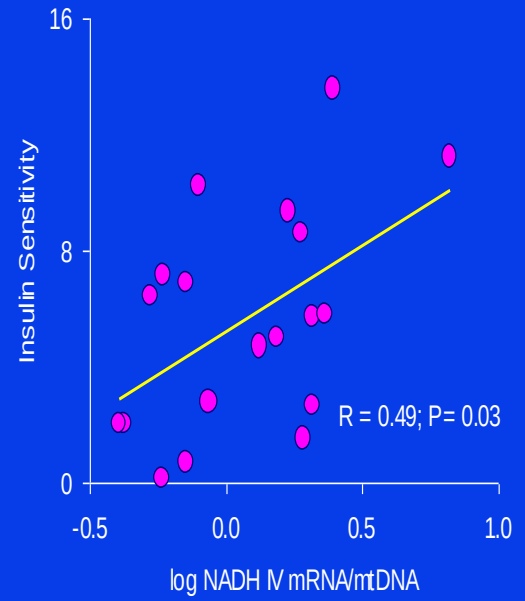


mtDNA and oxidative stress

Mitochondrial mRNA/mtDNA

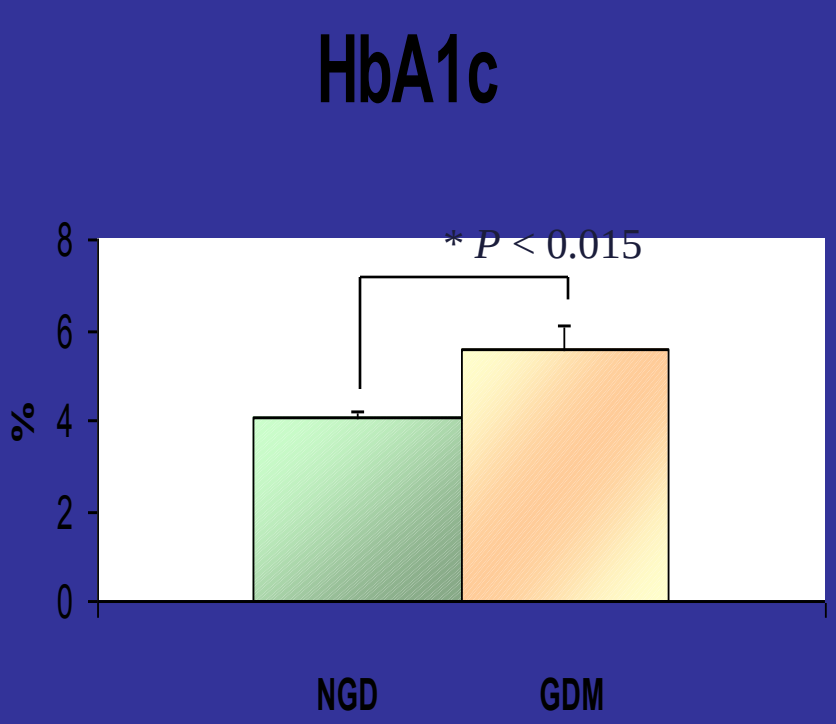


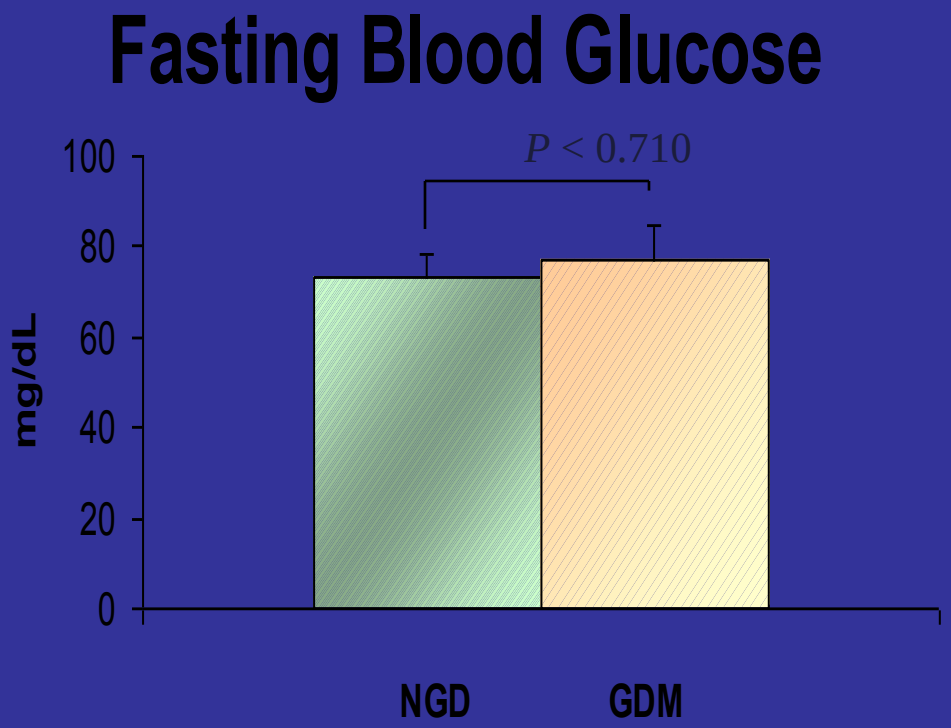
Correlation between mitochondrial gene expression and insulin sensitivity



Halvatsiotis et al, Diabetes 51:2395-2404, 2002

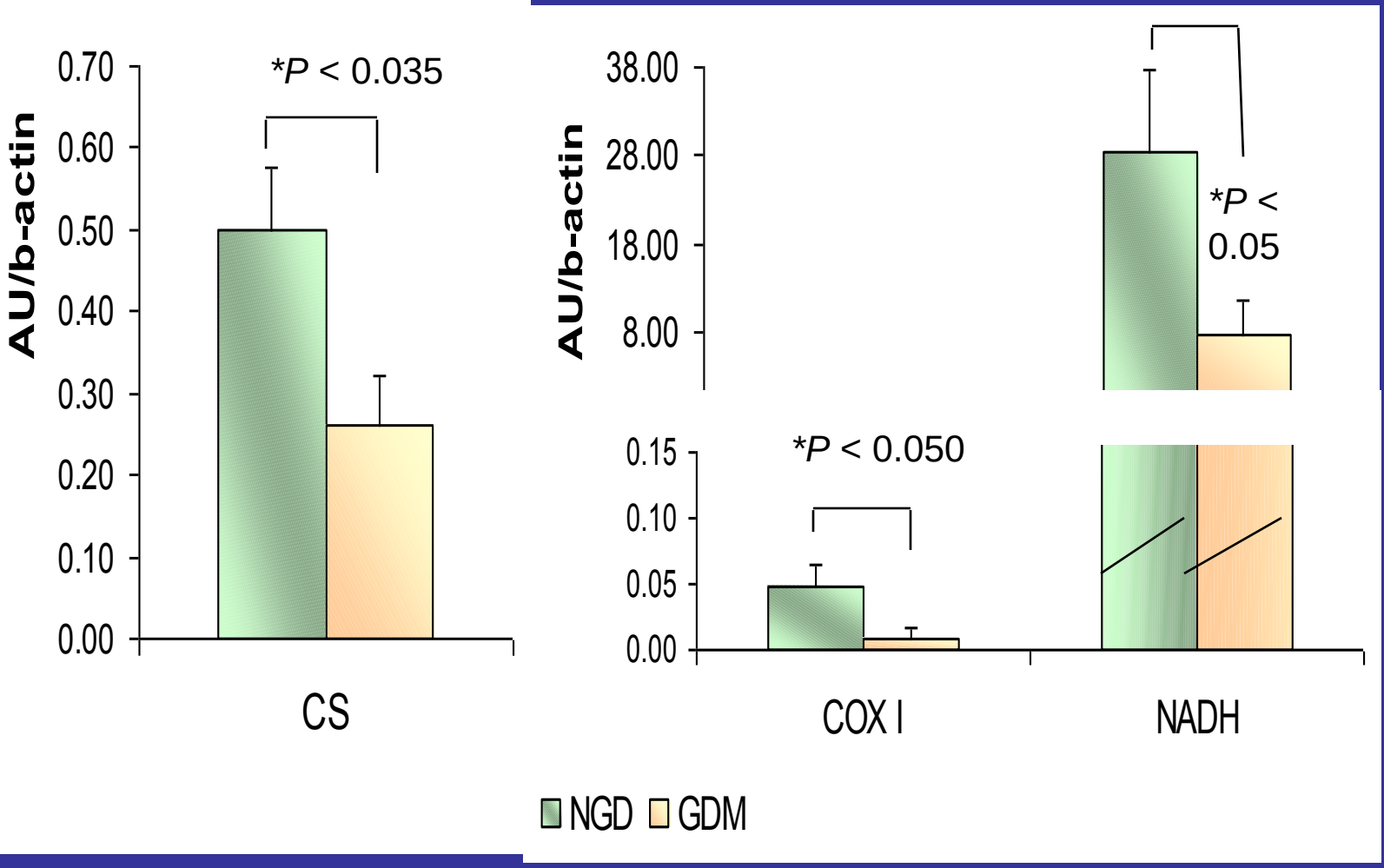
Gestational Diabetes





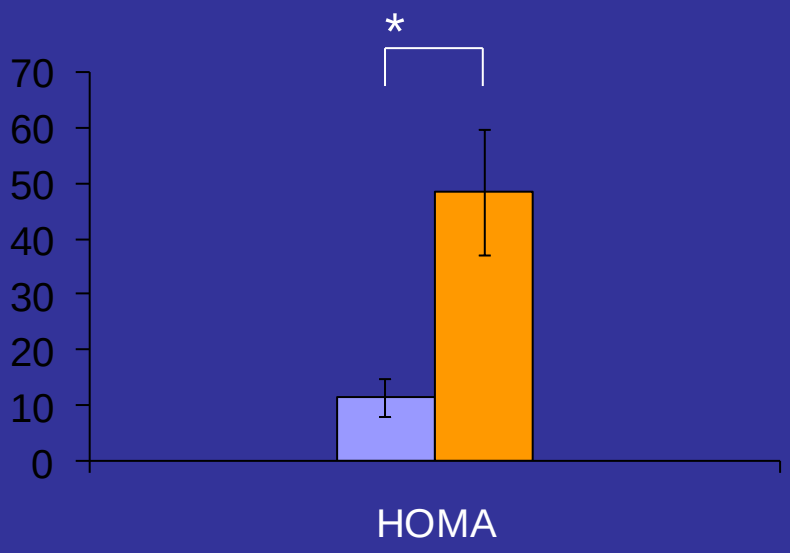
Halvatsiotis et al, 2008 *Unpublished data*

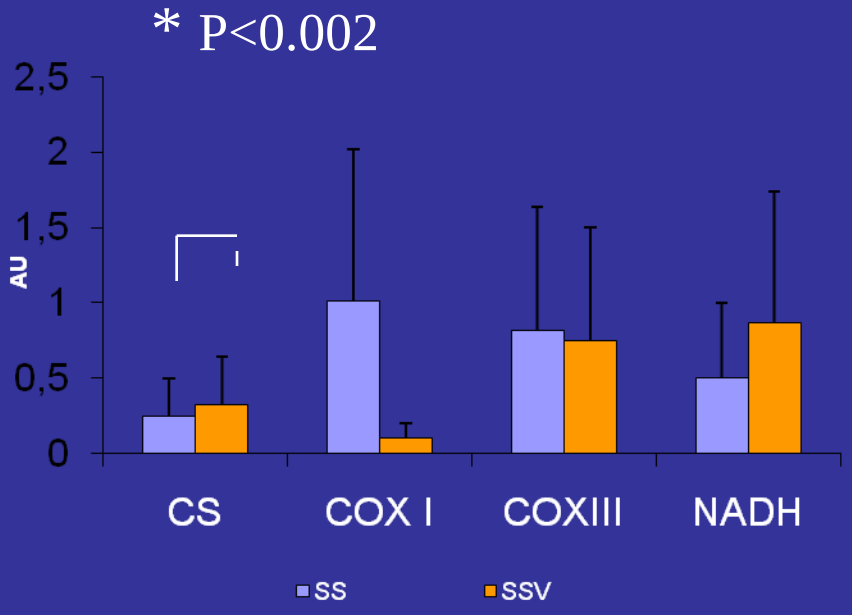
Placental
MITOCHONDRIAL ENZYME GENE EXPRESSION



Halvatsiotis et al, 2009 *Unpublished data*

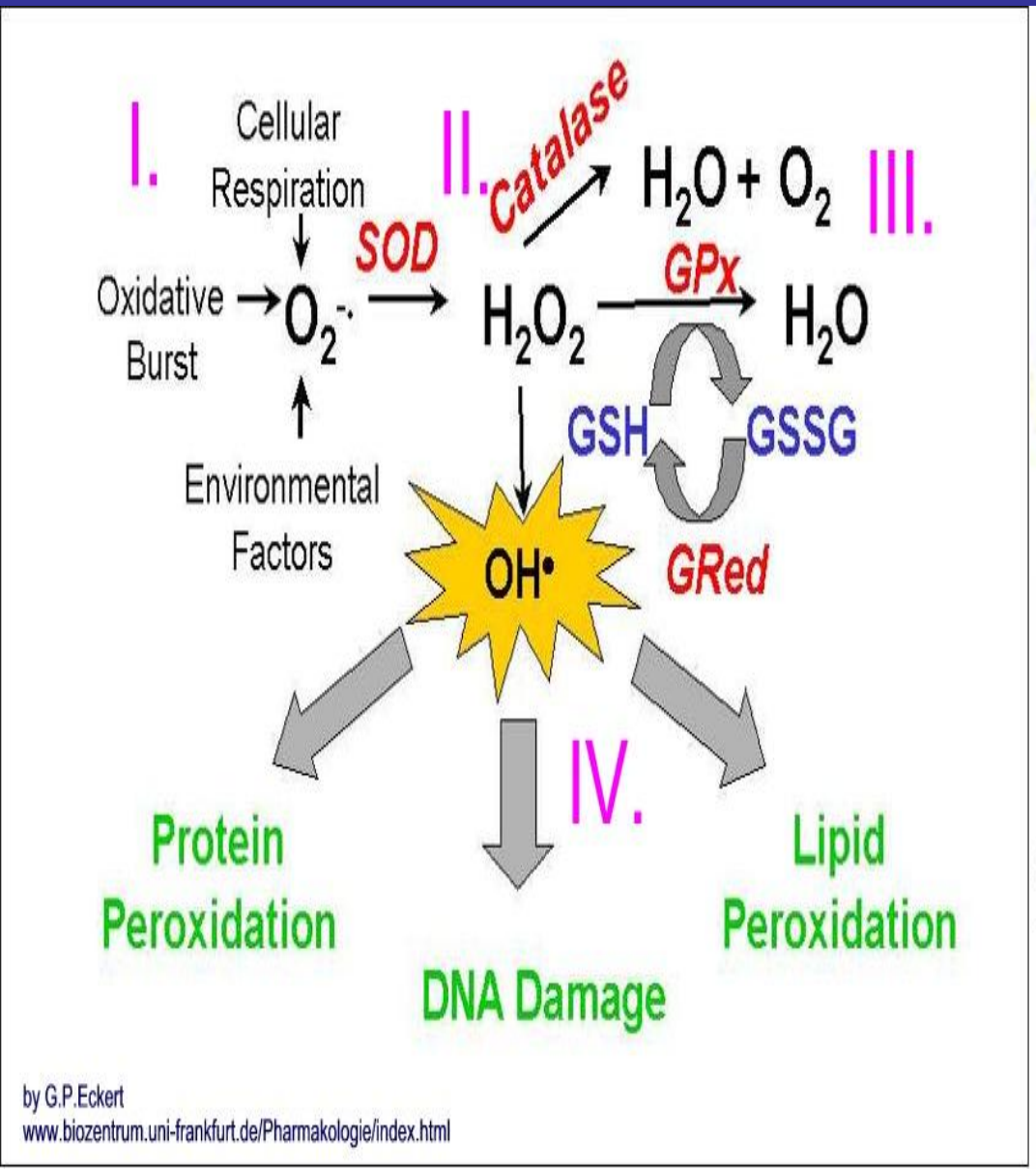
ΣΗΨΗ & ΜΙΤΟΧΟΝΔΡΙΑΚΗ ΔΥΣΛΕΙΤΟΥΡΓΙΑ

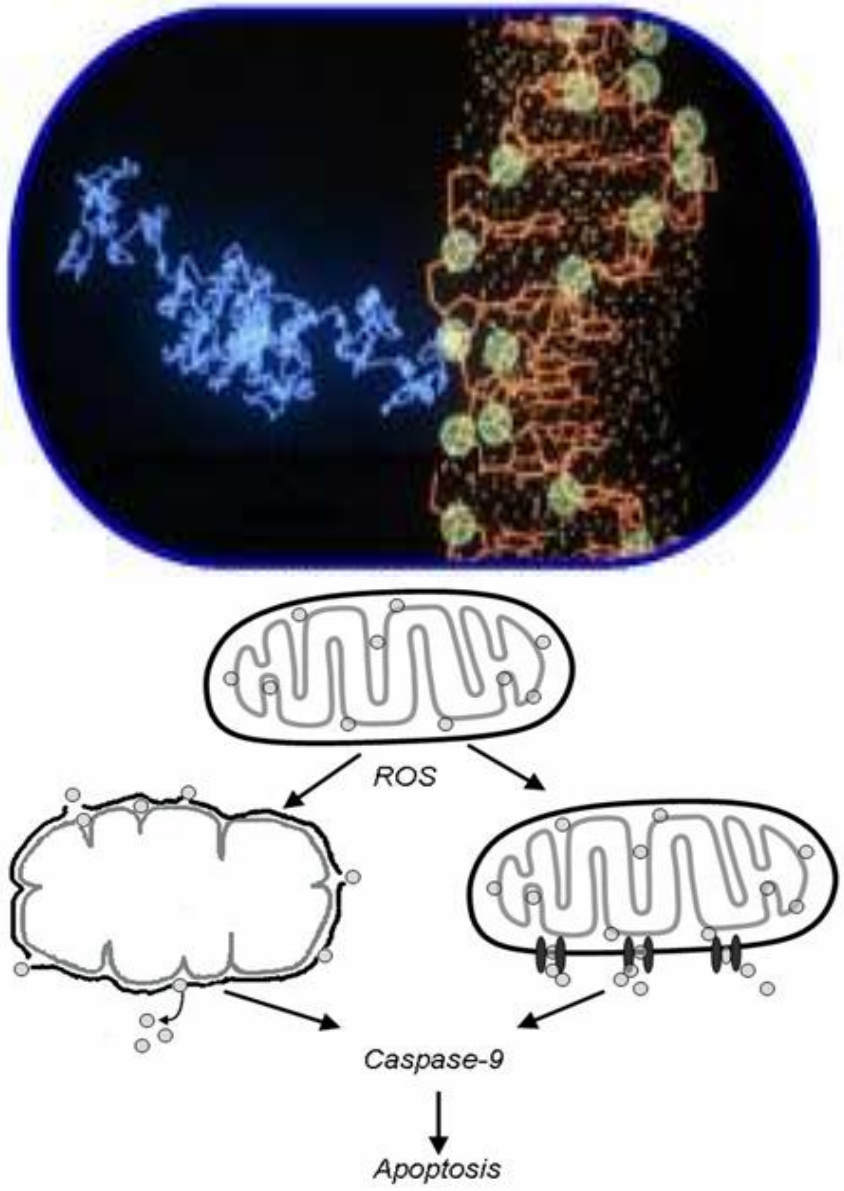




Halvatsiotis et al, 2007 *Unpublished data*

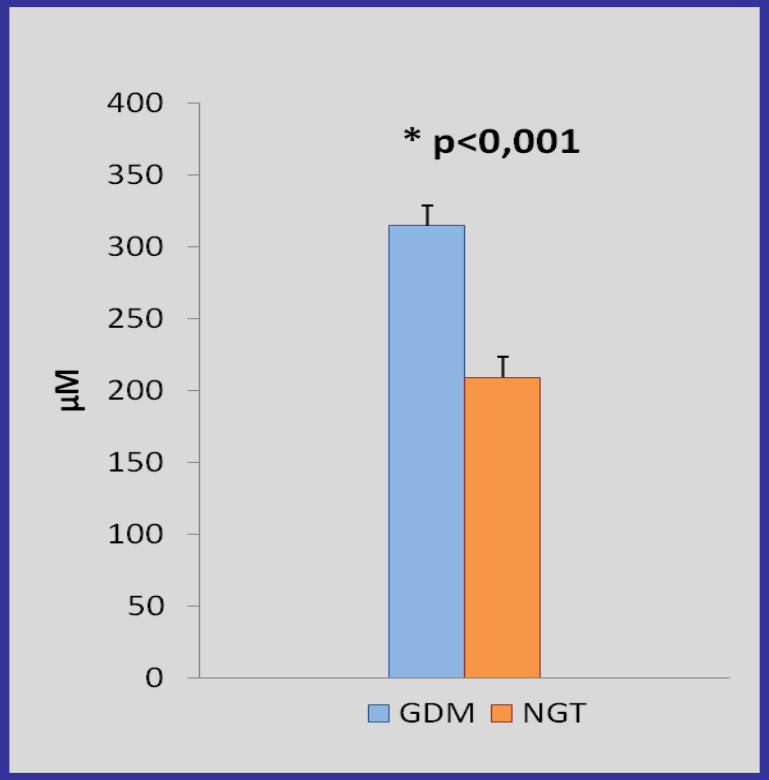
ΟΞΕΙΔΩΤΙΚΟ STRESS



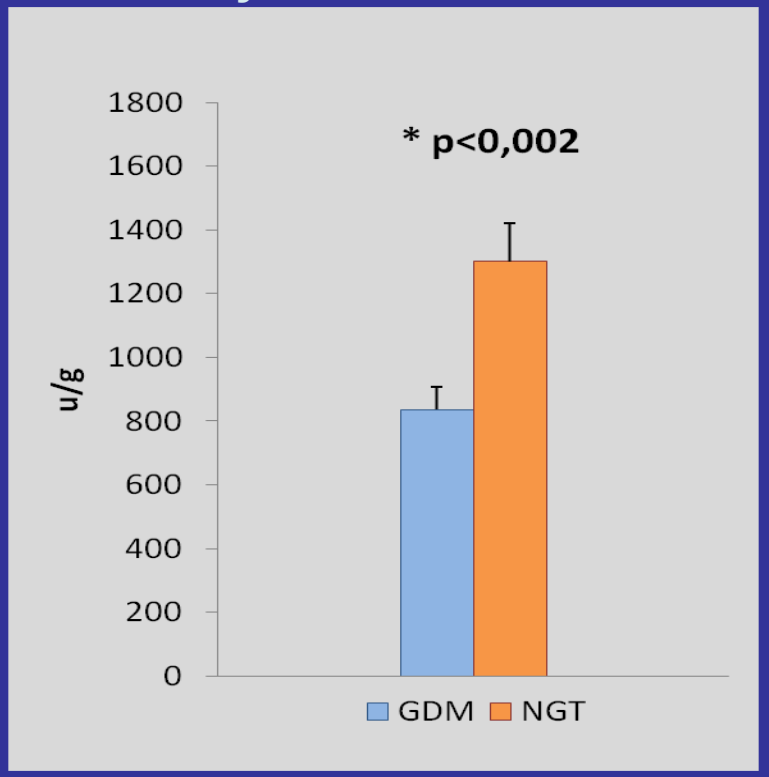


OXIDATIVE LOAD IN GESTATIONAL DIABETES

plasma hydrogen superoxide



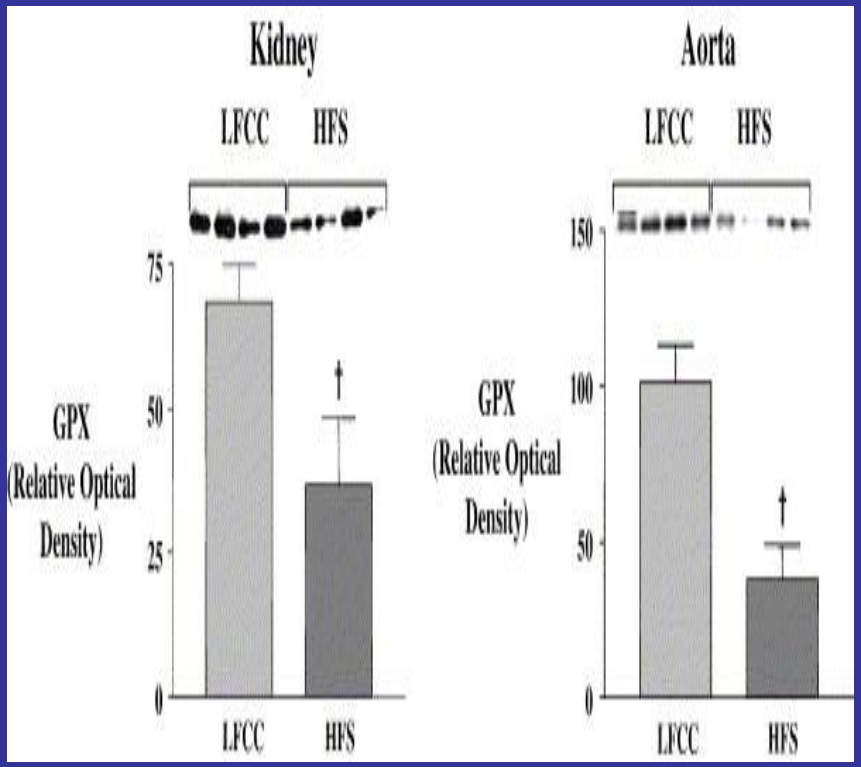
skeletal muscle SOD activity

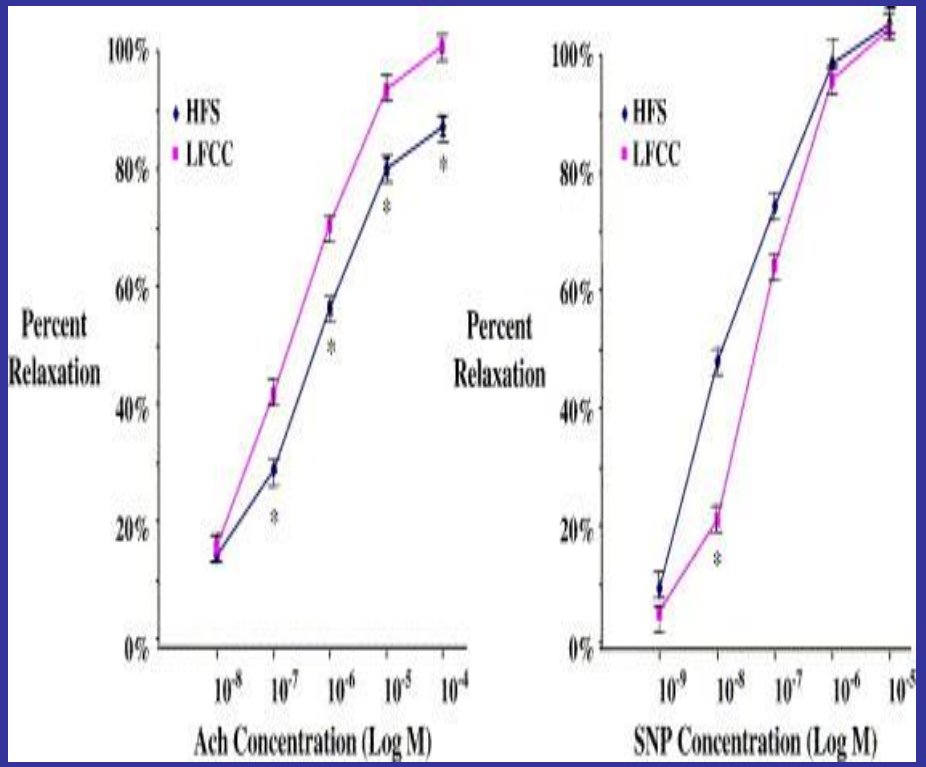


Halvatsiotis et al: American Diabetes Association Meeting 2010


ΔΥΣΛΙΠΙΔΑΙΜΙΑ
ΚΑΡΔ.ΑΝΕΠΑΡΚΕΙΑ
Σ.ΔΙΑΒΗΤΗΣ
ΚΑΠΝΙΣΜΑ
ΥΠΕΡΤΑΣΗ
ΟΜΟΚΥΣΤΕΪΝΗ
↑O2
NO↓
ΕΝΔΟΘΗΛΙΑΚΗ ΔΥΣΛΕΙΤΟΥΡΓΙΑ
ΑΠΟΠΤΩΣΗ
ΛΕΙΕΣ ΜΥΪΚΕΣ ΙΝΕΣ
ΥΠΕΡΤΡΟΦΙΑ
ΥΠΕΡΠΛΑΣΙΑ
ΑΓΓΕΙΟΣΥΣΤΟΛΗ
ΟΞΕΙΔΩΣΗ
ΛΙΠΙΔΙΑ
ΠΡΩΤΕΪΝΕΣ
DNA
ΘΡΟΜΒΟΓΕΝΕΣΗ
ΣΥΓΚΟΛΗΣΗ
ΛΕΥΚΟΚΥΤΤΑΡΩΝ

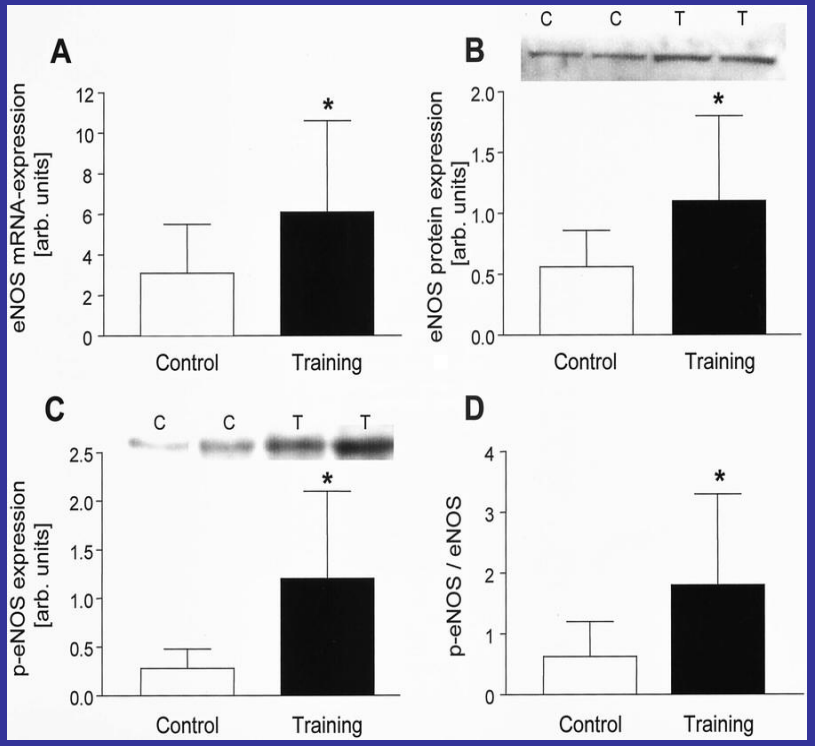
ΟΞΕΙΔΩΤΙΚΟ STRESS & ΔΙΑΤΑΣΙΜΟΤΗΤΑ ΑΓΓΕΙΩΝ

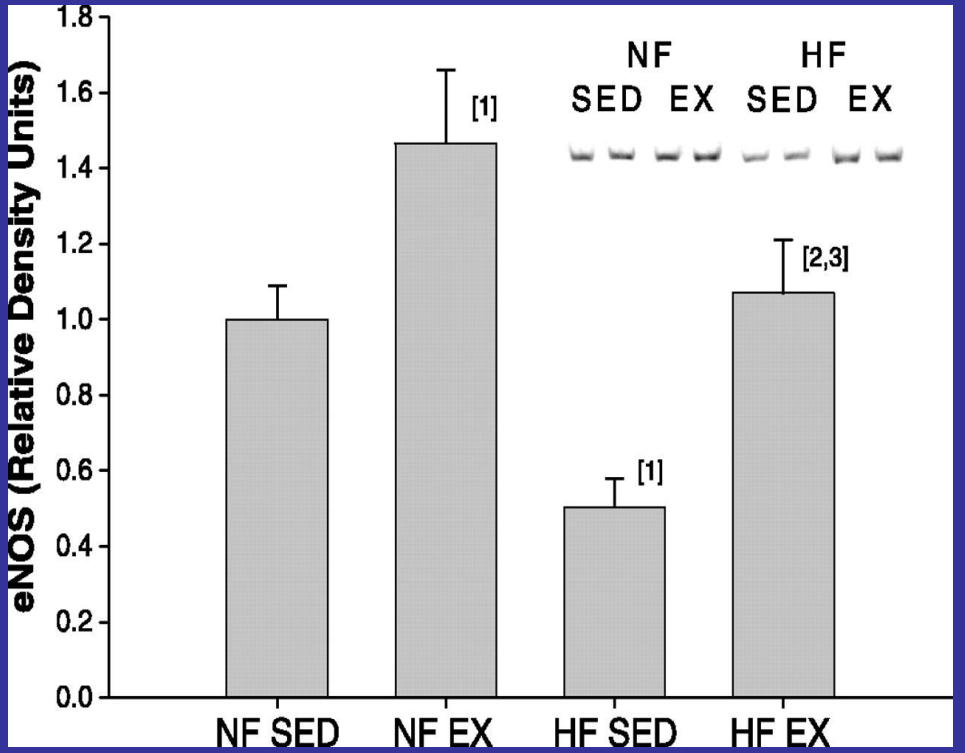




Roberts et al, Metabolism 2006, 55:928-34

ΑΣΚΗΣΗ & NO

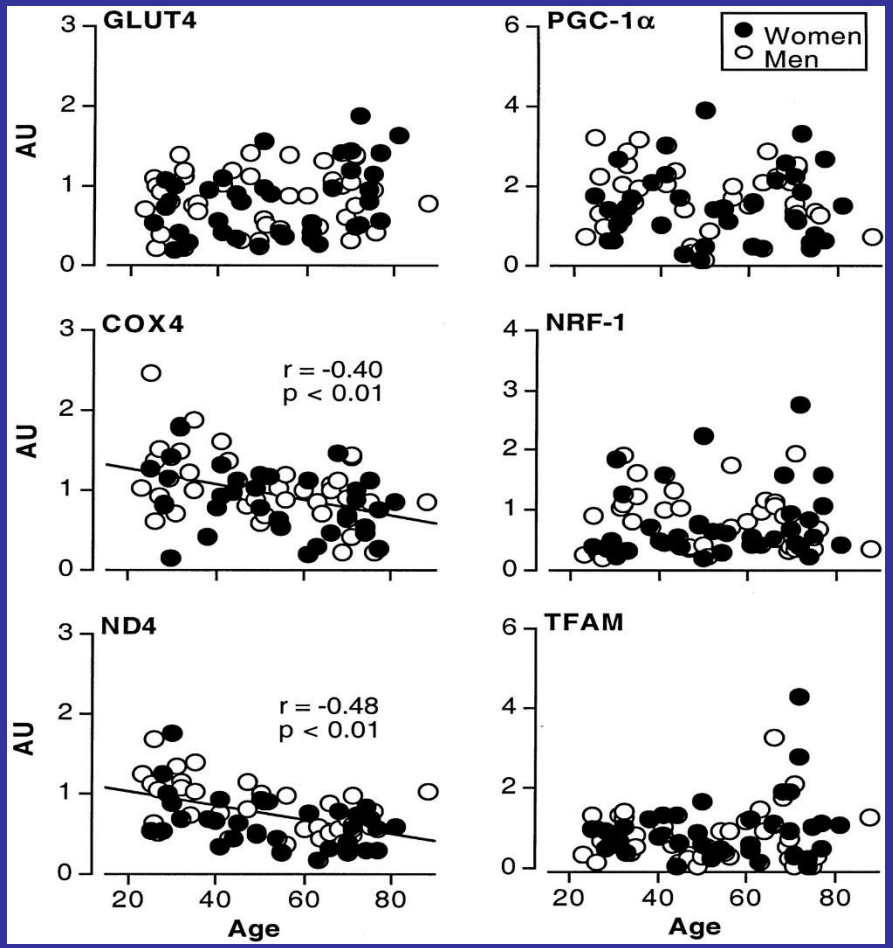


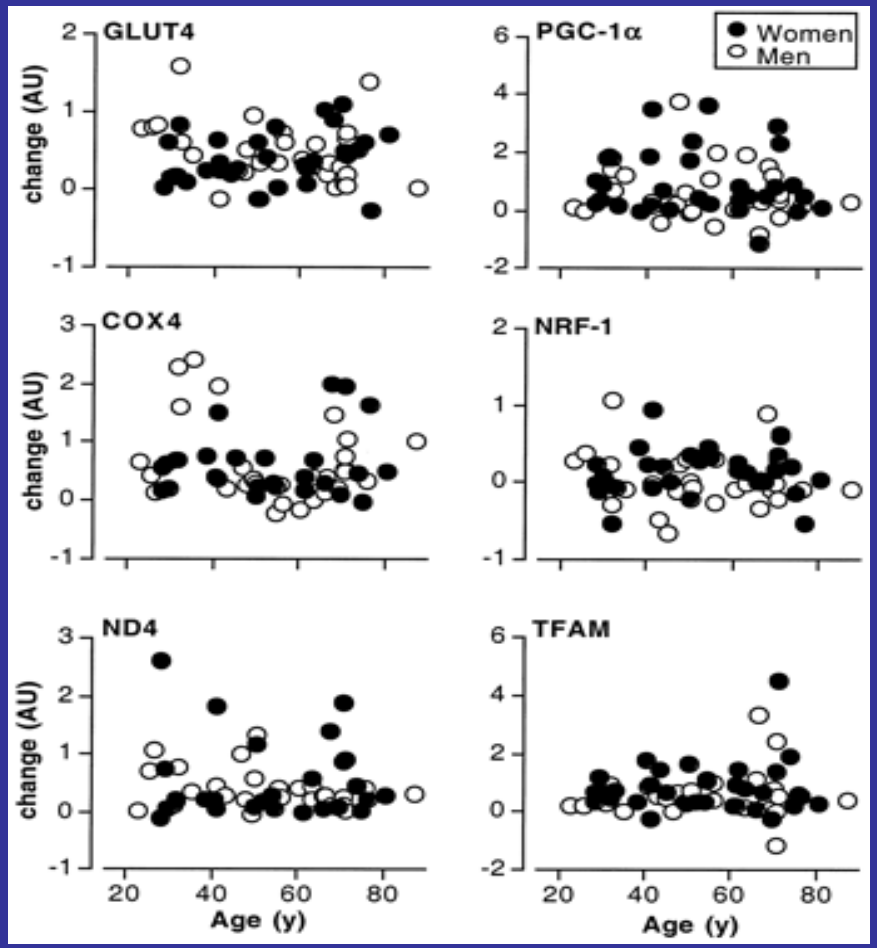


Halbrecht et al,
Circulation 2003, 107:3152-8

Henderson et al,
J Appl Physiol, 2004, 97:1159-1168

ΠΡΙΝ & ΜΕΤΑ ΤΗΝ ΑΣΚΗΣΗ

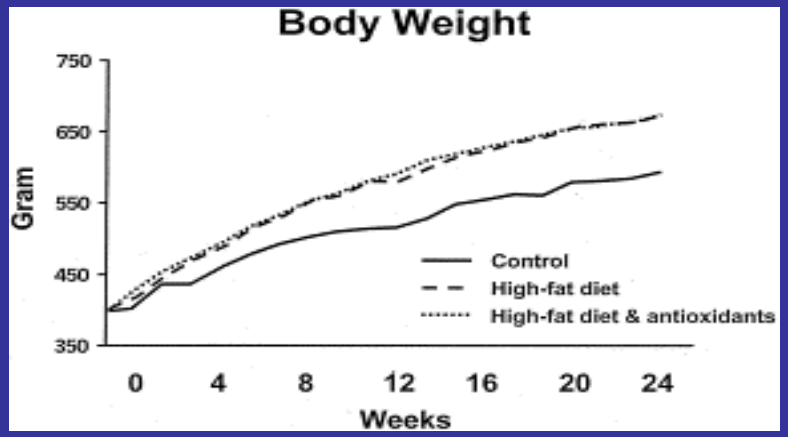


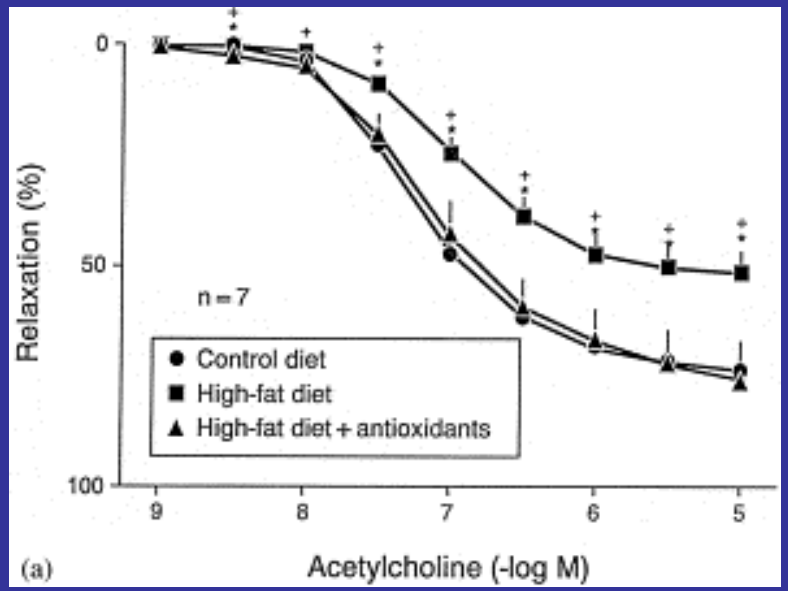


Short et al, Diabetes, 2004 52:1888-96


Φυσική Δραστηριότητα
Διατροφή
Ενδοκυττάρια
Γλυκόζη
ΕΛΟ
ΟΞΕΙΔΩΤΙΚΟ STRESS
ΓΕΝΕΤΙΚΗ ΠΡΟΔΙΑΘΕΣΗ
Δυσλειτουργία Ενδοθηλίου Μυοκαρδίου
Καρδιαγγειακά Νοσήματα
Μυϊκός ιστός
Λιπώδης ιστός
Ινσουλινοαντίσταση
Μεταβολικό Σύνδρομο
β-Κύτταρο
Ινσουλινοέκκριση
Μεταγευματική Υπεργλυκαιμία
Σακχαρώδης Διαβήτης

ΑΝΤΙΟΞΕΙΔΩΤΙΚΑ ΣΥΜΠΛΗΡΩΜΑΤΑ

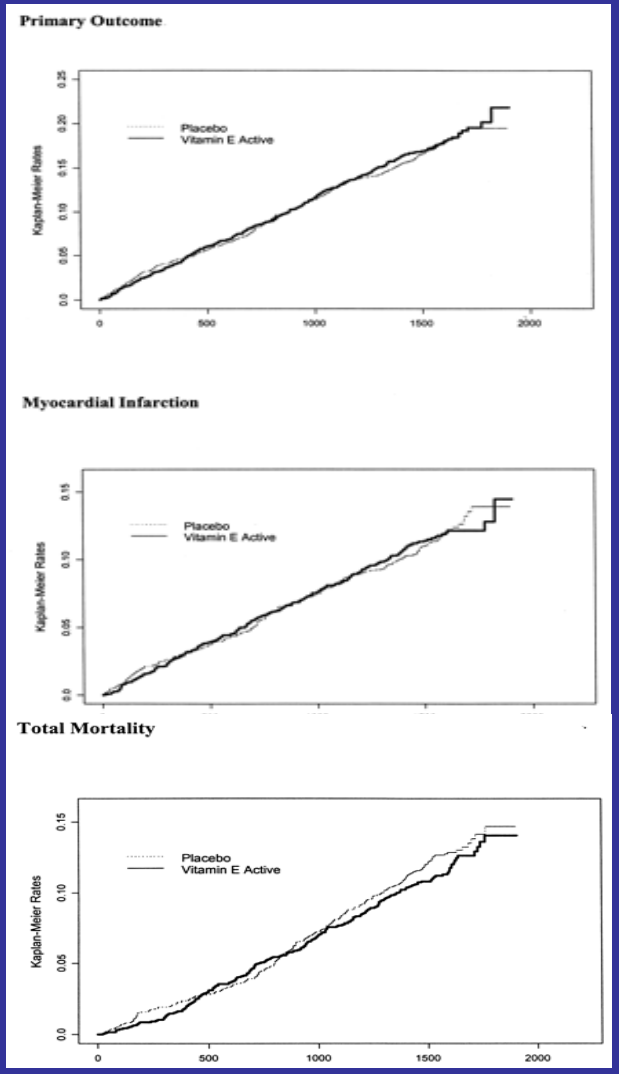




- Επίμυες
- Παχυσαρκία, τροφή υψηλή σε λιπαρά
- Vit. A,E & Selenium
- Παρασκευάσματα αορτής αντίδραση σε phenylephrine & acetylcholine
- Παθολογική εξαρτώμενη στο ενδοθήλιο διατασιμότητα
- Vit περιόρισαν την αγγειακή δυσλειτουργία σε παρόμοια επίπεδα λιπιδίων & ινσουλίνης

J.Sato et al,
Atherosclerosis 161:327-333, 2002

HOPE study
& MICRO-HOPE sub study

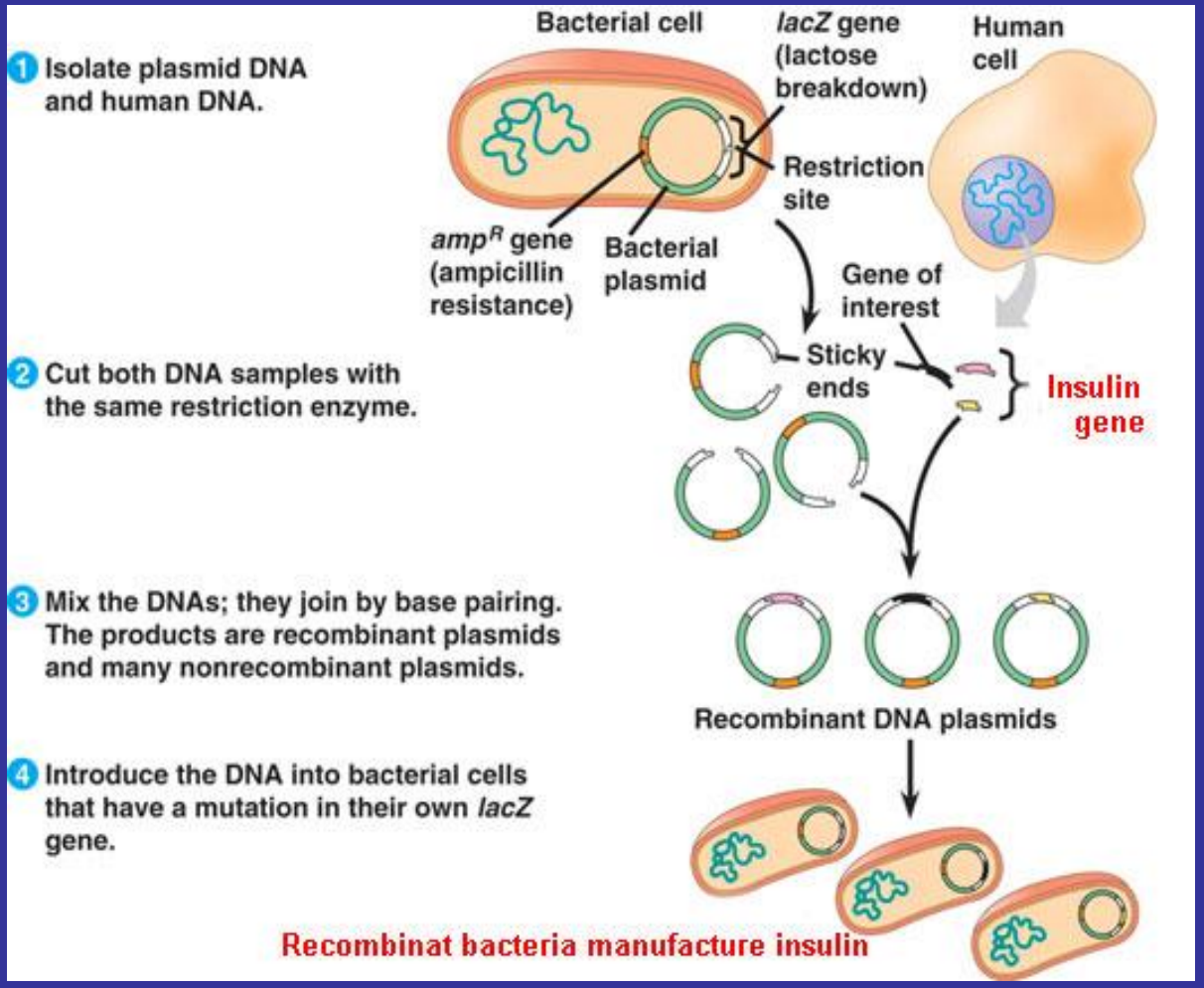


- Vit E (400 iu) & ramipril σε καρδιαγγειακά συμβάματα
- 9.541 pt για 4.5 έτη (3.654 διαβητικοί)
- Καμιά διαφορά στους πρωτογενείς στόχους της μελέτης (ΕΜ, ΑΕΕ, θάνατος), GHBA1c, νεφρική λειτουργία, θνησιμότητα
- Πιθανά πολύ αργά στην εξέλιξη της αθηρομάτωσης για την αναστροφή των βλαβών

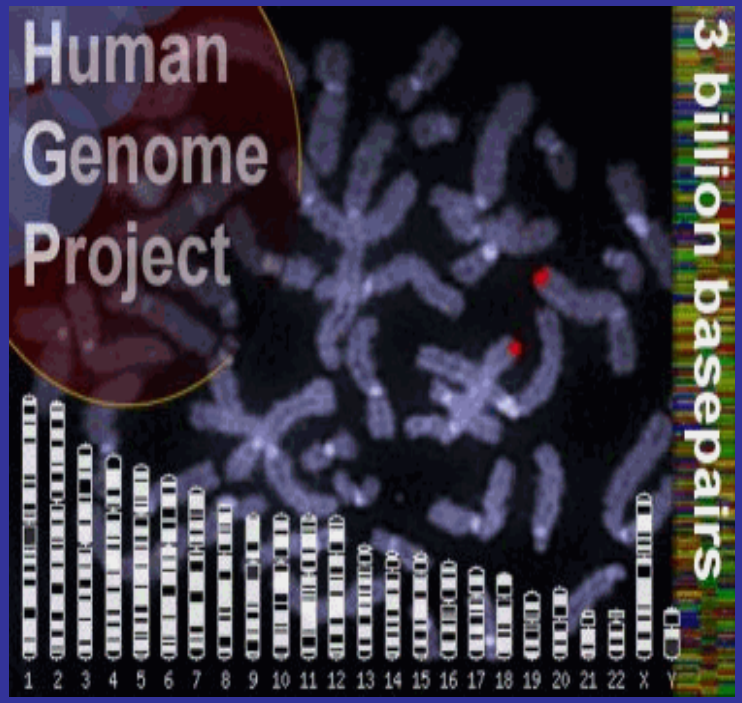
Lonn E. et al

Diabetes Care 25:1919-1927, 2002

ΠΡΩΪΜΗ ΓΟΝΙΔΙΑΚΗ ΠΑΡΕΜΒΑΣΗ

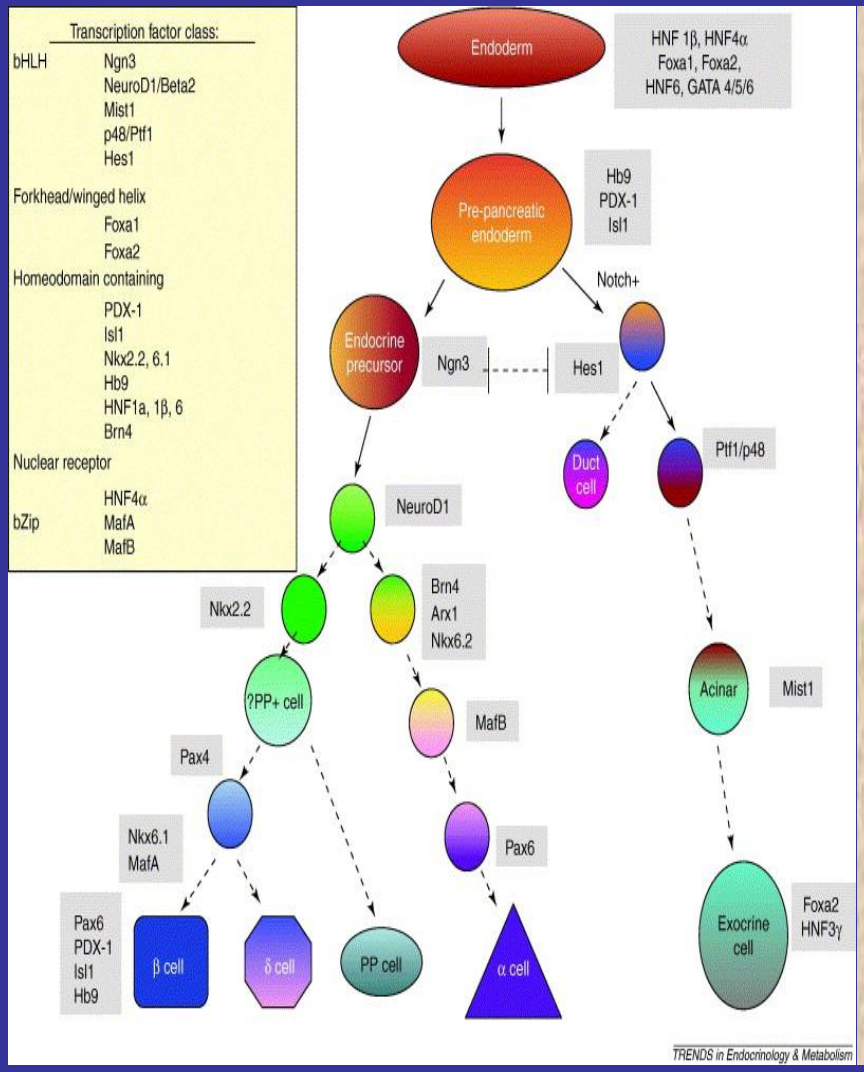


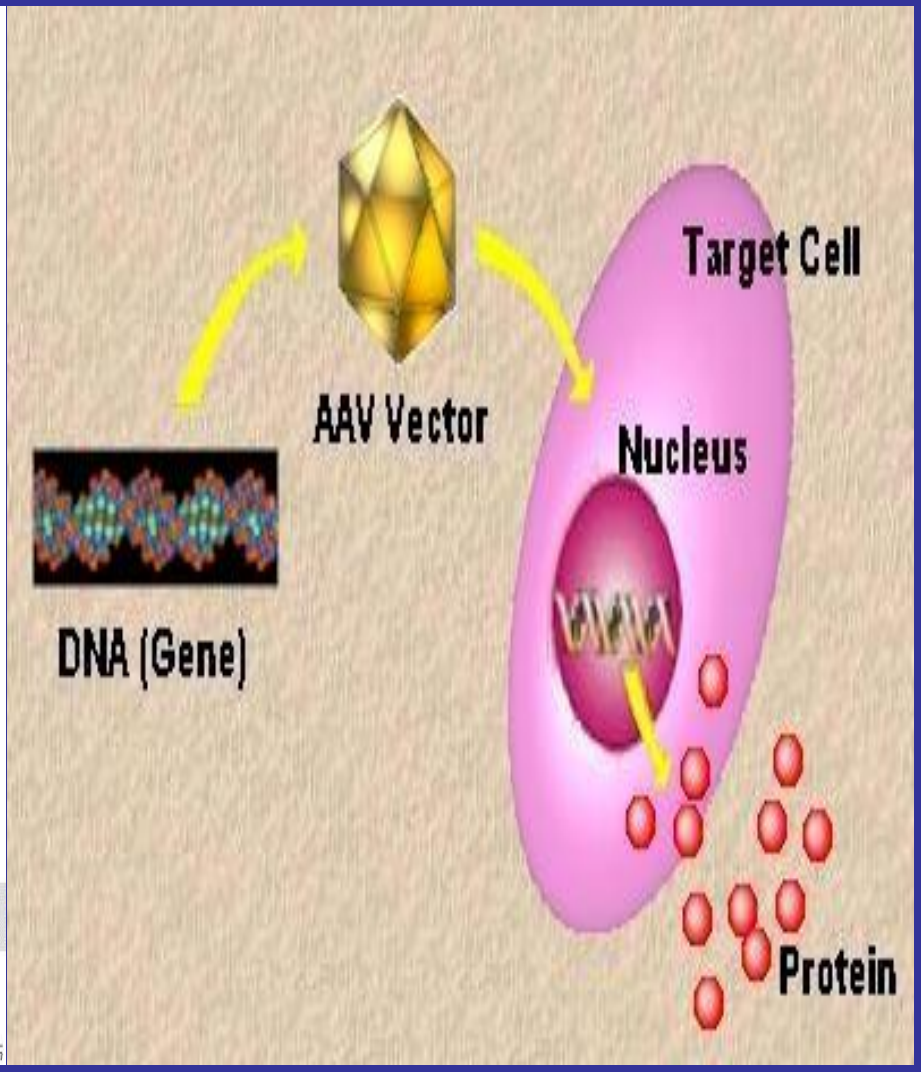
ΓΟΝΙΔΙΑΚΗ ΘΕΡΑΠΕΙΑ ΣΤΟΝ ΔΙΑΒΗΤΗ - ΠΡΟΣΠΑΘΕΙΕΣ



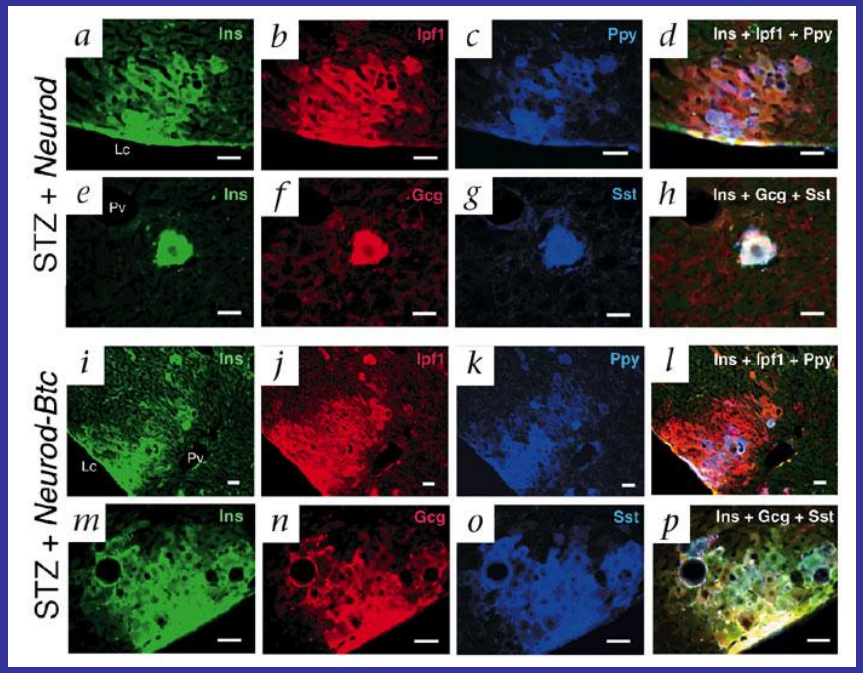
- ΜΕΘΟΔΟΣ ΧΟΡΗΓΗΣΗΣ ΤΟΥ ΓΕΝΕΤΙΚΟΥ ΥΛΙΚΟΥ (αδενοϊοί-ρετροϊοί)
- ΤΡΟΠΟΠΟΙΗΣΗ ΛΕΙΤΟΥΡΓΙΩΝ ΜΗ β-ΚΥΤΤΑΡΩΝ ΓΙΑ ΕΚΤΟΠΗ ΠΑΡΑΓΩΓΗ ΙΝΣΟΥΛΙΝΗΣ (ηπατοκύτταρα, Κ-κύτταρα)
- ΜΕΤΑΤΡΟΠΗ ΑΡΧΕΓΟΝΩΝ ΒΛΑΣΤΙΚΩΝ ΠΡΟΓΟΝΙΚΩΝ Ή ΑΛΛΩΝ ΚΥΤΤΑΡΩΝ ΣΕ β- ΚΥΤΤΑΡΑ

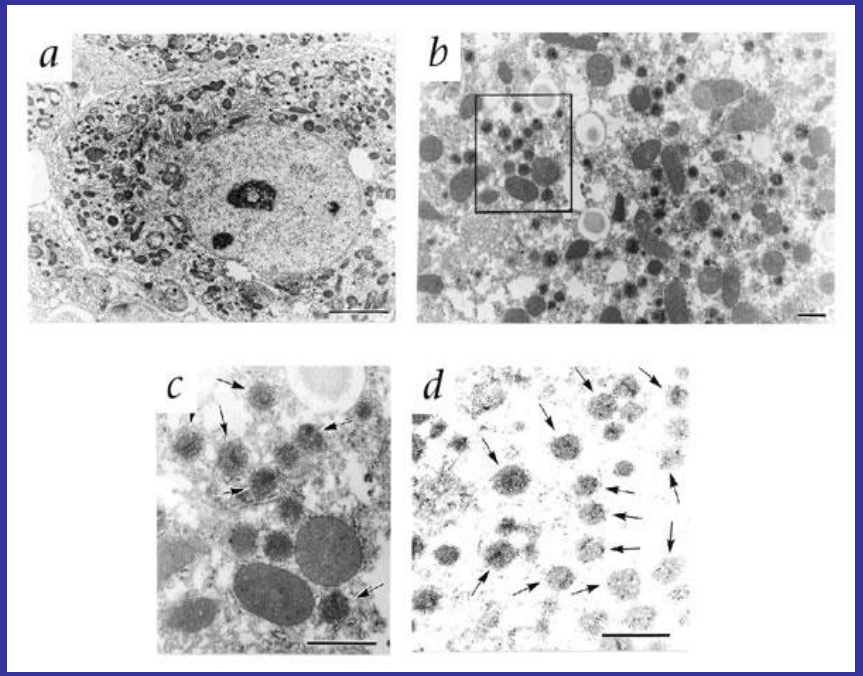
DIABETES GENE THERAPY





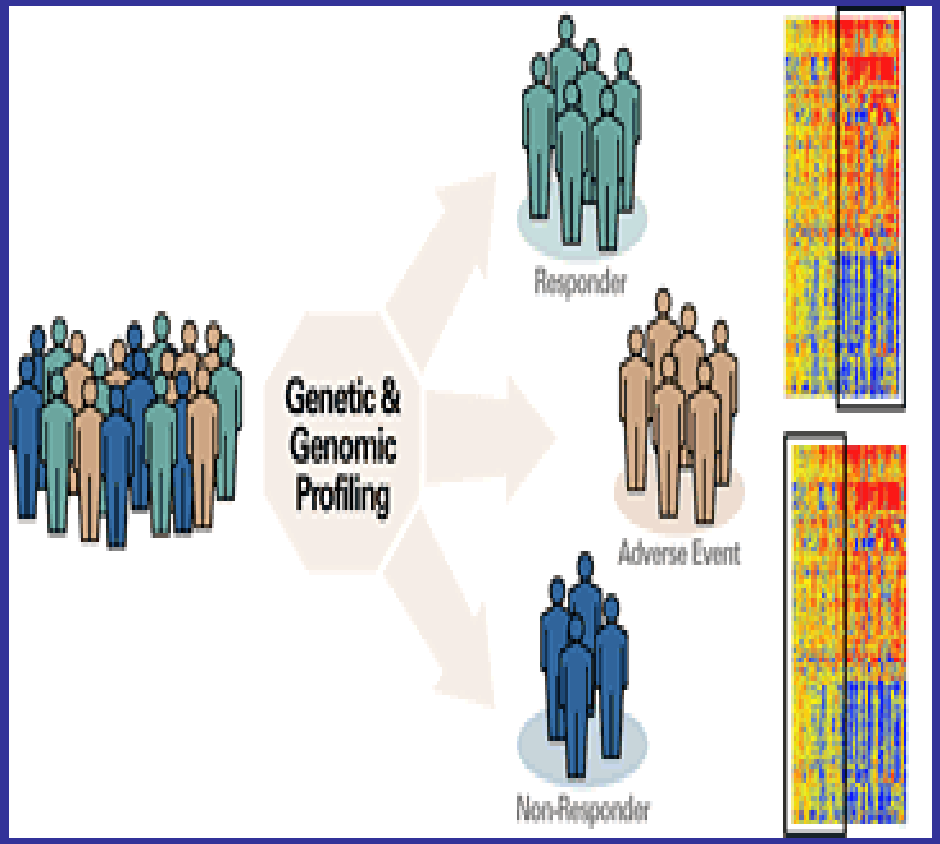
ΠΑΡΑΓΩΓΗ ΙΝΣΟΥΛΙΝΗΣ ΑΠΟ ΗΠΑΤΟΚΥΤΤΑΡΑ

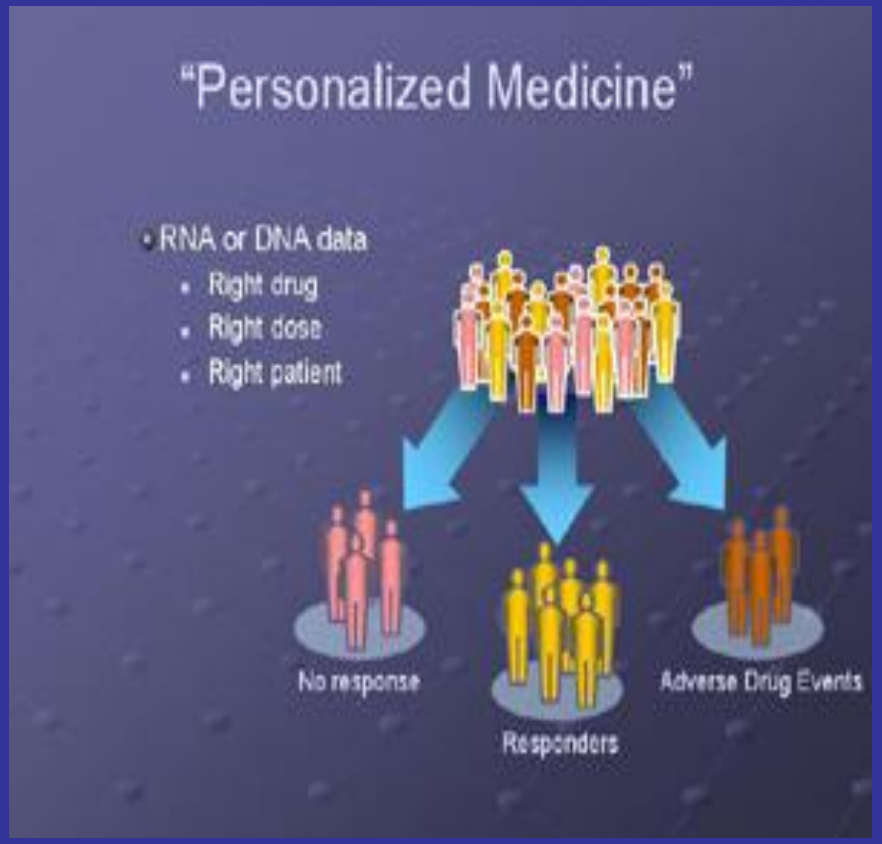




Kojima et al, Nature Medicine 9, 596-603, 2003

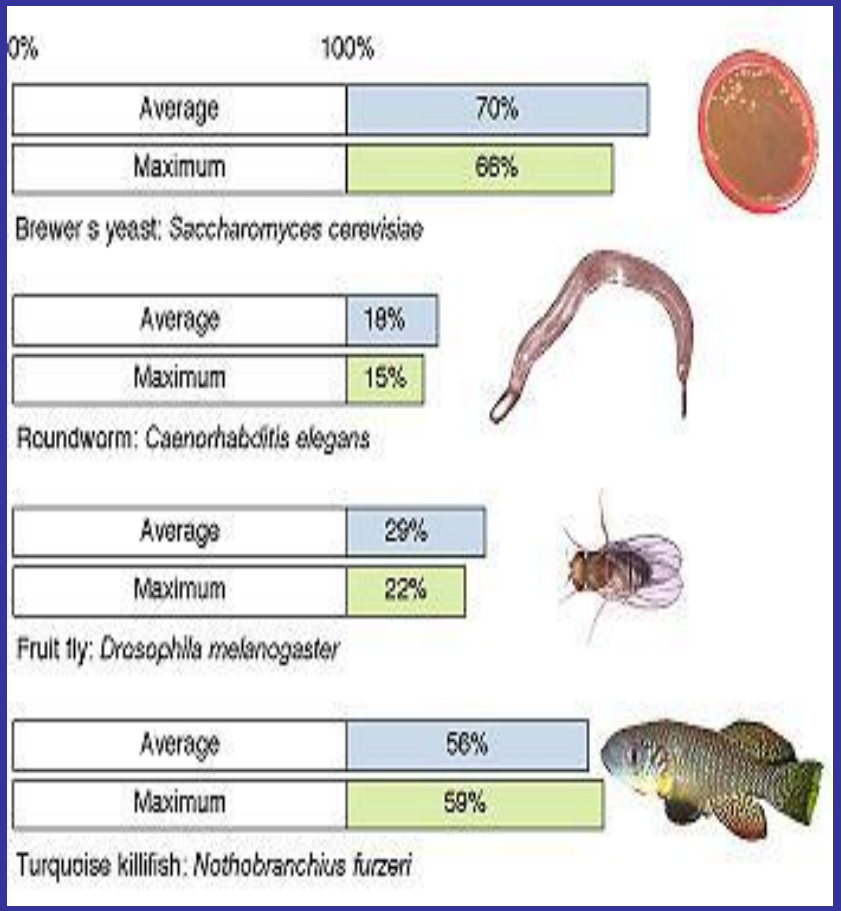
PHARMACOGENOMICS



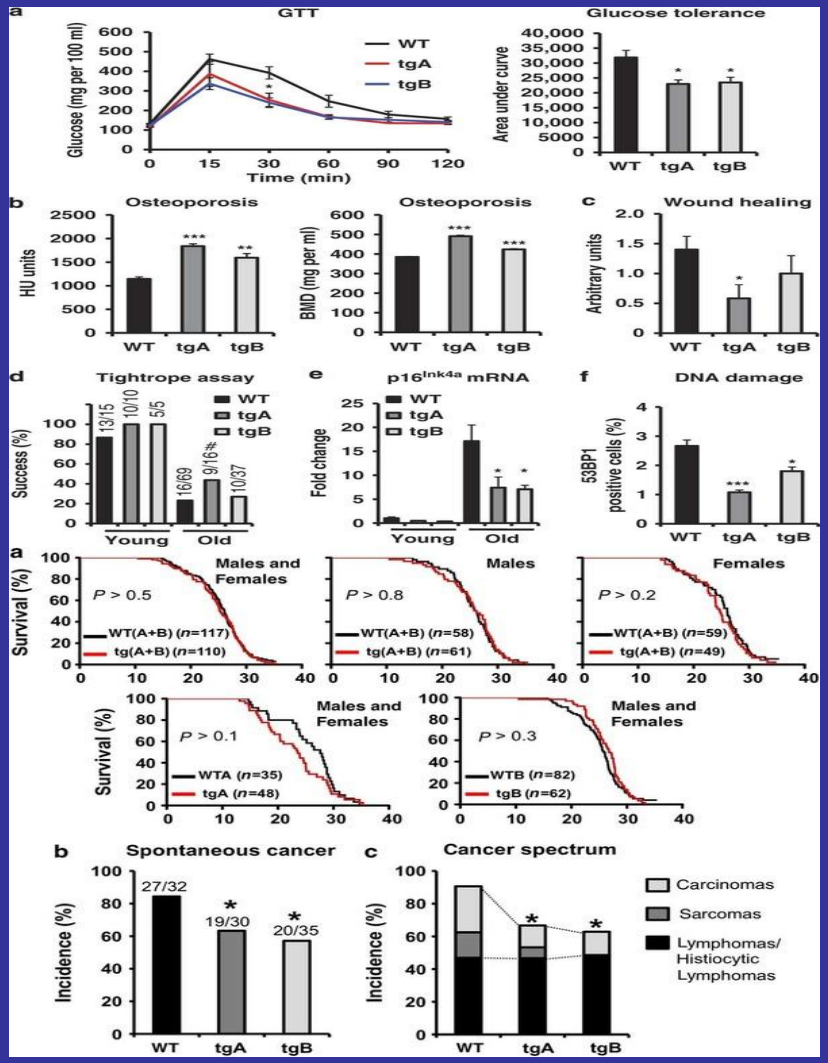


LIFE EXTENSION & Sir2

(Silent information regulator 2)

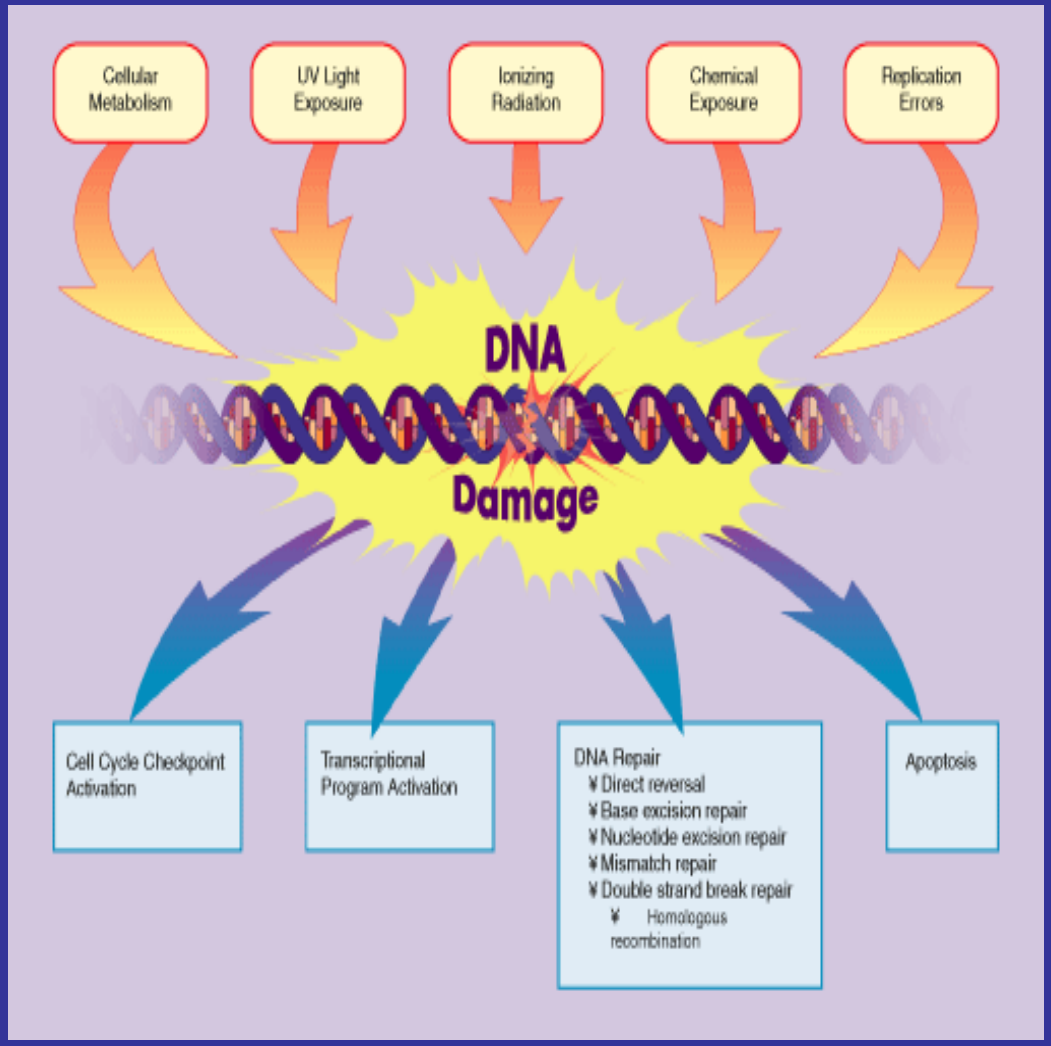


Bauer et al, Nat Rev Drug Disc 5:493-06, 2006



Heranz et al, Nature Communications 1: 3 DOI: doi:10.1038/ncomms1001

SIRT6 & επιδιόρθωση του DNA



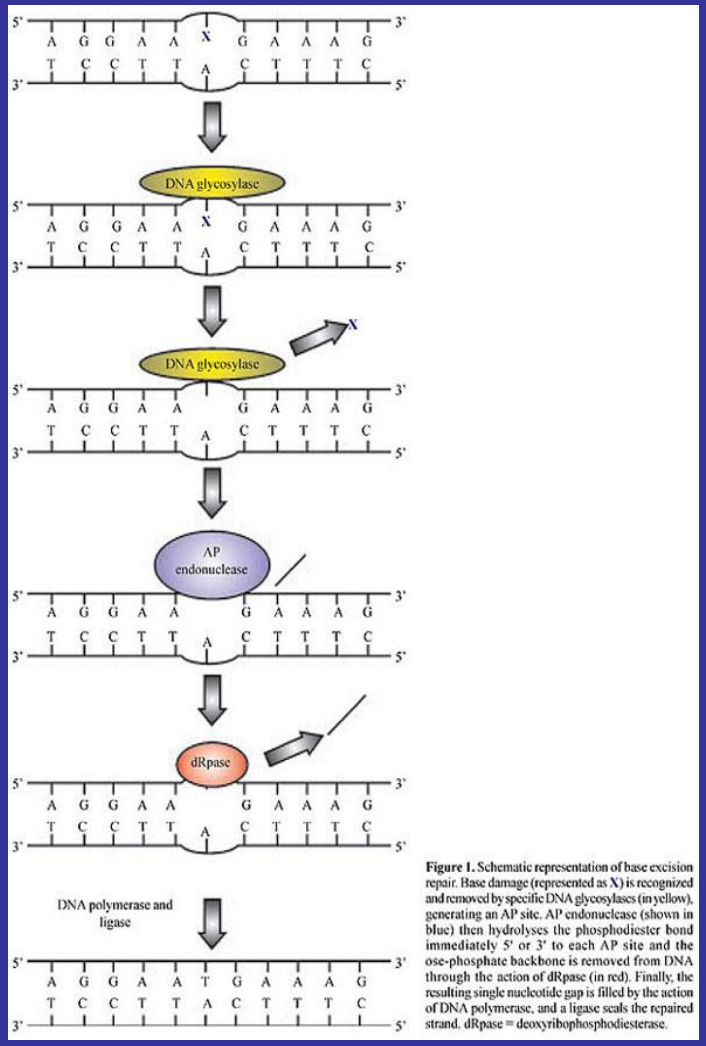
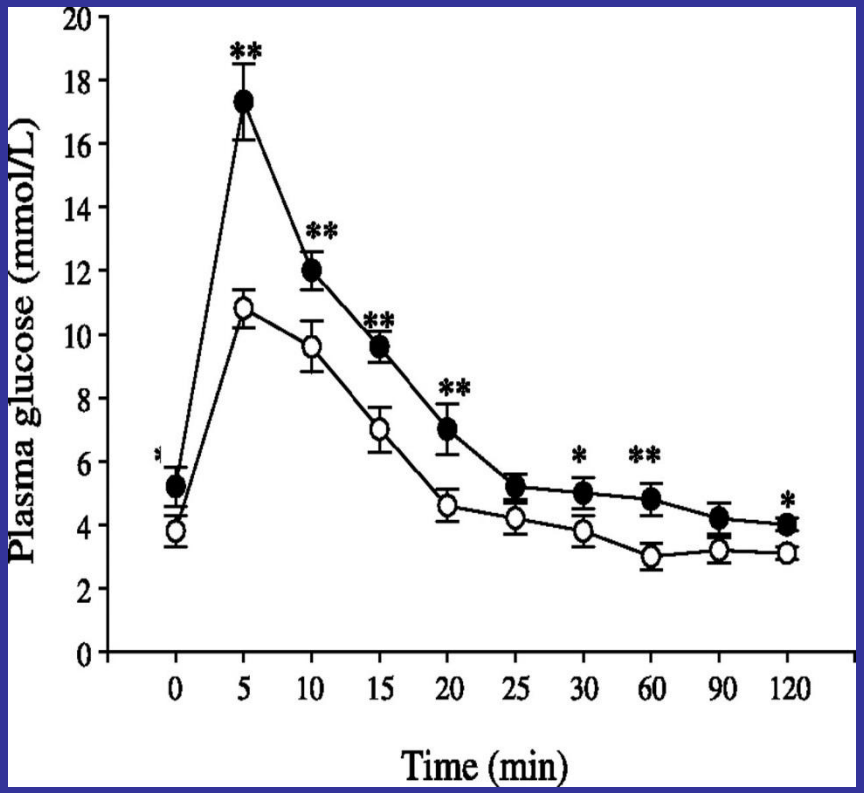
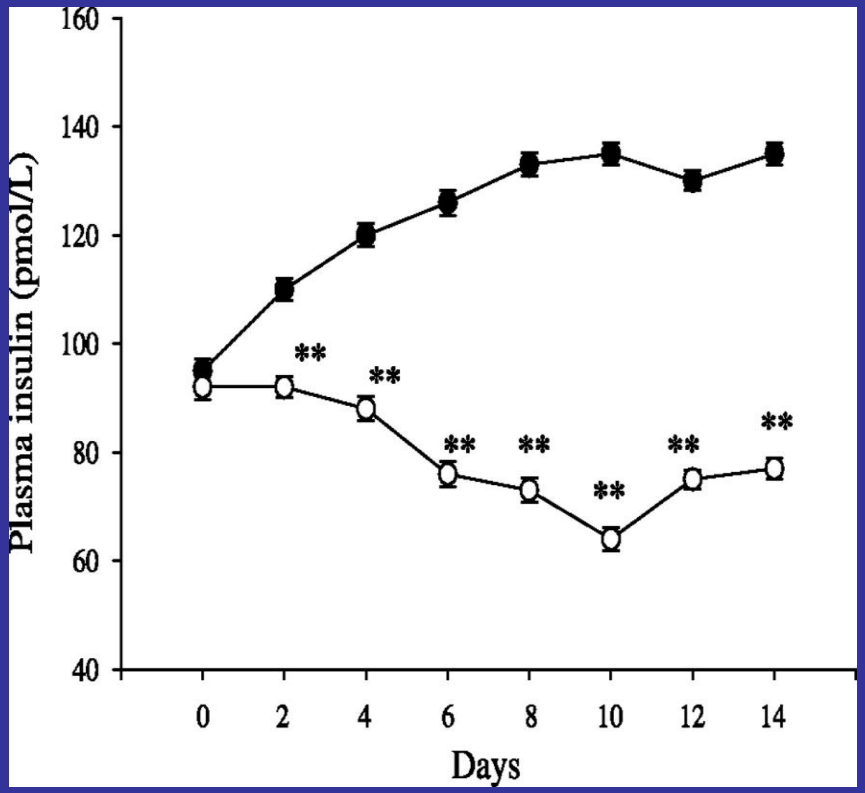


Figure 1. Schematic representation of base excision repair. Base damage (represented as X) is recognized and removed by specific DNA glycosylases (in yellow), generating an AP site. AP endonuclease (shown in blue) then hydrolyses the phosphodiester bond immediately 5' or 3' to each AP site and the ose-phosphate backbone is removed from DNA through the action of dRpase (in red). Finally, the resulting single nucleotide gap is filled by the action of DNA polymerase, and a ligase seals the repaired strand. dRpase = deoxyribophosphodiesterase.

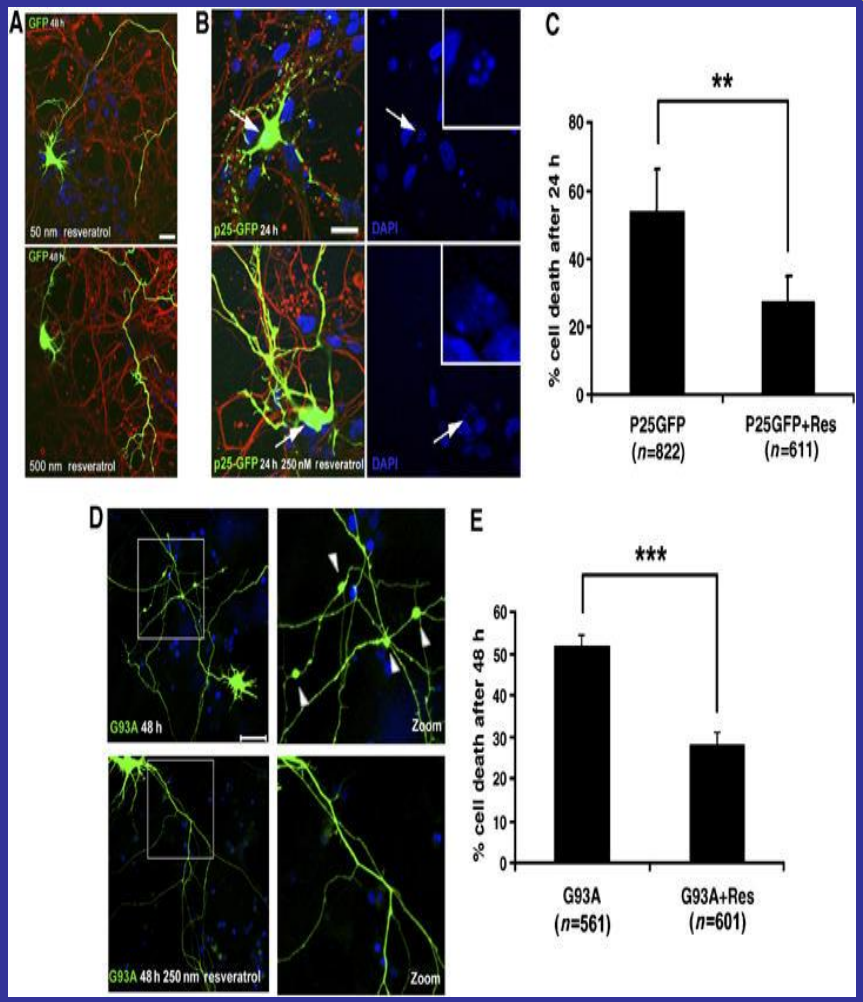
RESVERATROL
& Μεταβολισμός γλυκόζης

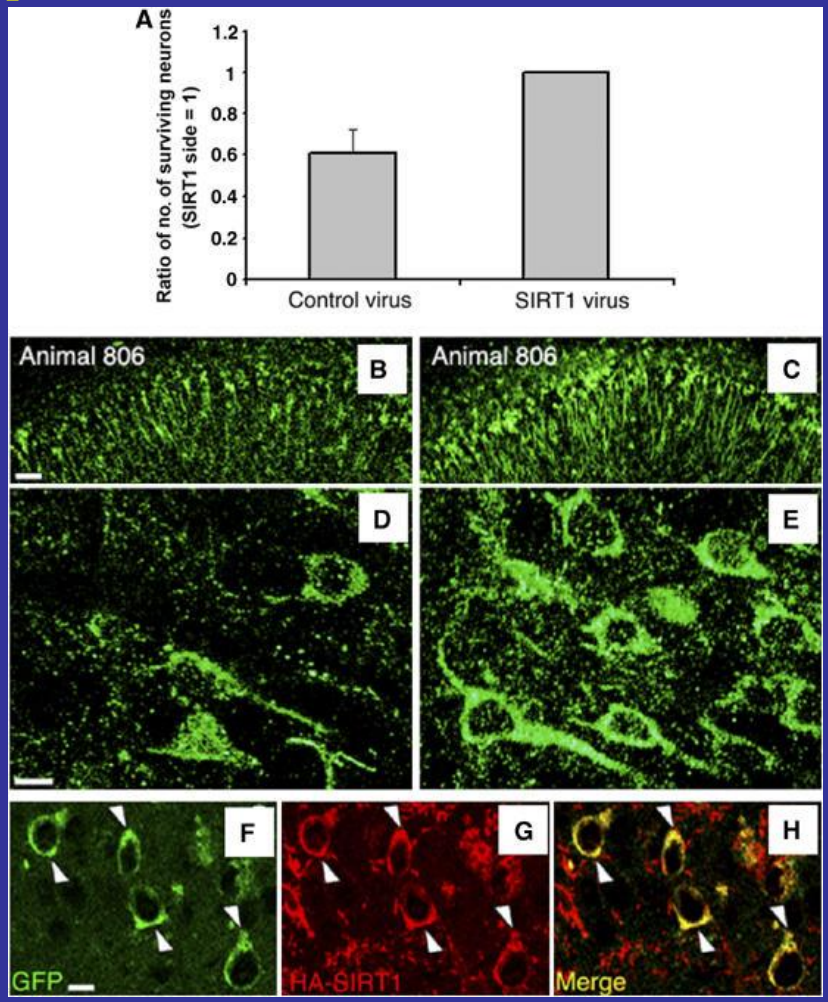




Hui – Chen et al, Am J Physiol Endocrinol Metab 290:1339-46, 2006

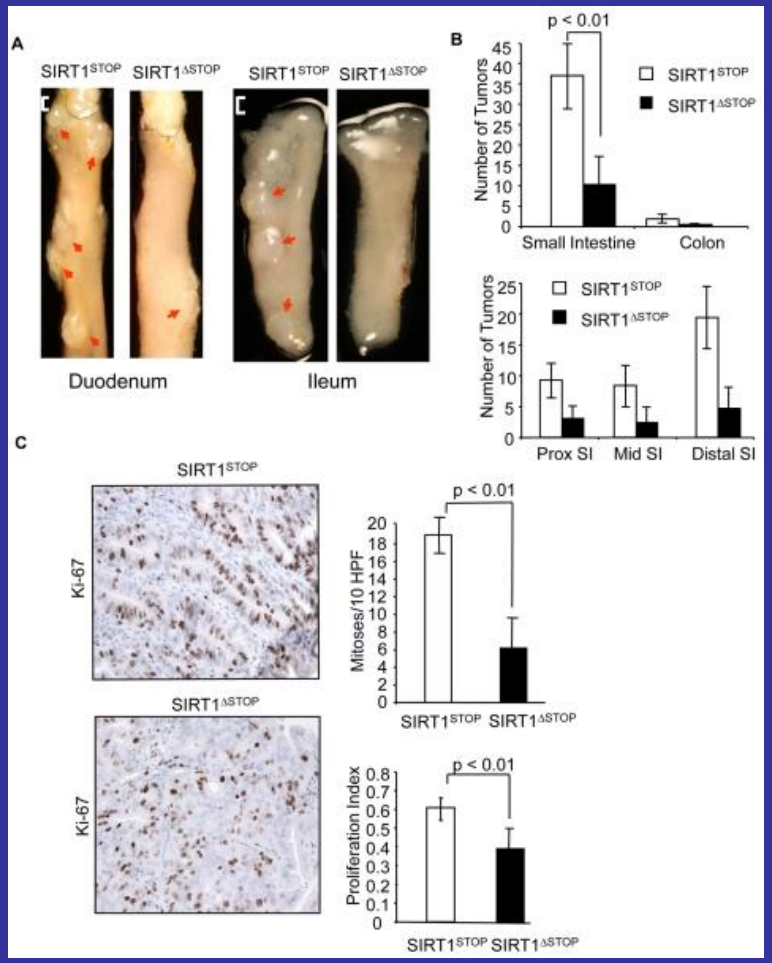
Resveratrol & Νευροεκφυλιστικά νοσήματα





Kim et al, EMBO J. 2007 July 11; 26(13): 3169–3179

Resveratrol & Καρκίνος



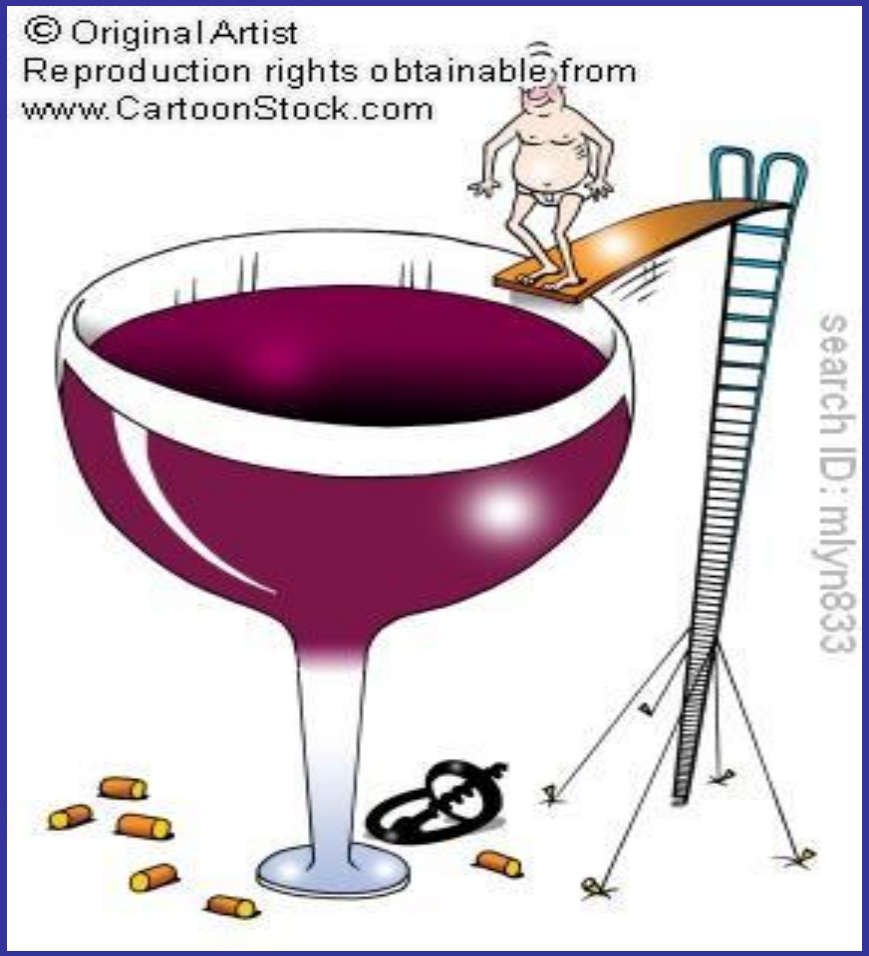
Firestein et al PLoS ONE. 2008; 3(4): e2020.

Δέρματος Μελάνωμα
Μαστού Πνεύμονα
Στομάχου εντέρου Παχέος
Παγκρέατος Οισοφάγου
Ηπάτωμα Προστάτη
Νευροβλάστωμα
Ινοβλάστωμα
Λευχαιμία

Athar et el,
Toxicol Appl Pharmacol. 2007 ; 224(3): 274–283.

«Πηγές» Resveratrol

- Κόκκινα σταφύλια
- Φραγκοστάφυλα
- Φυστίκια
- Βατόμουρα



«ΡΟΔΙΝΟ» ΜΕΛΛΟΝ

ΔΙΑΒΗΤΗΣ – ΠΑΧΥΣΑΡΚΙΑ
ΚΑΡΔΙΟΠΑΘΕΙΕΣ
ΚΑΚΟΗΘΕΙΕΣ
ΝΕΥΡΟΕΚΦΥΛΙΣΤΙΚΕΣ ΝΟΣΟΙ
ΓΗΡΑΝΣΗ