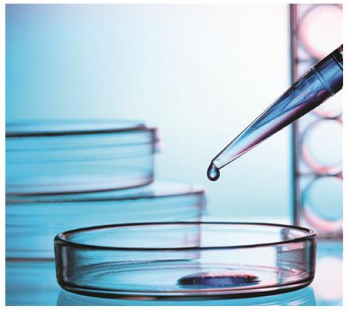
JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING

HNRCA



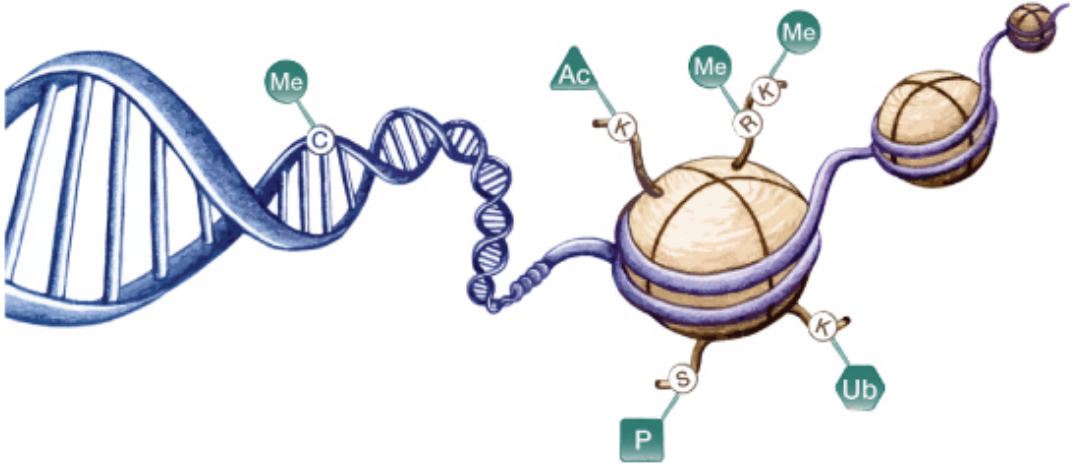
Jose M Ordovas
JM-USDA-HNRCA at Tufts

Genotypes and Disease Risk: What Do We Currently Know about Nutrition and Epigenetics?

December, 2017

Tufts UNIVERSITY

Genome versus Epigenome



The total length of the human genome is over **3 billion base pairs**. The genome is organized into 22 paired chromosomes, plus the X chromosome (one in males, two in females) and, in males only, one Y chromosome.

Genetic Variation

Last Updated: Build 150 (Feb 3, 2017)

RefSNP Count: **325.7 Million**

SubSNP Count: 907.2 Million

Residing within the human genome are approximately **30 million CpG dinucleotides** which are unmethylated, hemi-methylated or abundantly methylated; varying according to region on chromosome, alleles, type of cell or phase of development

NUTRITION

GENOME

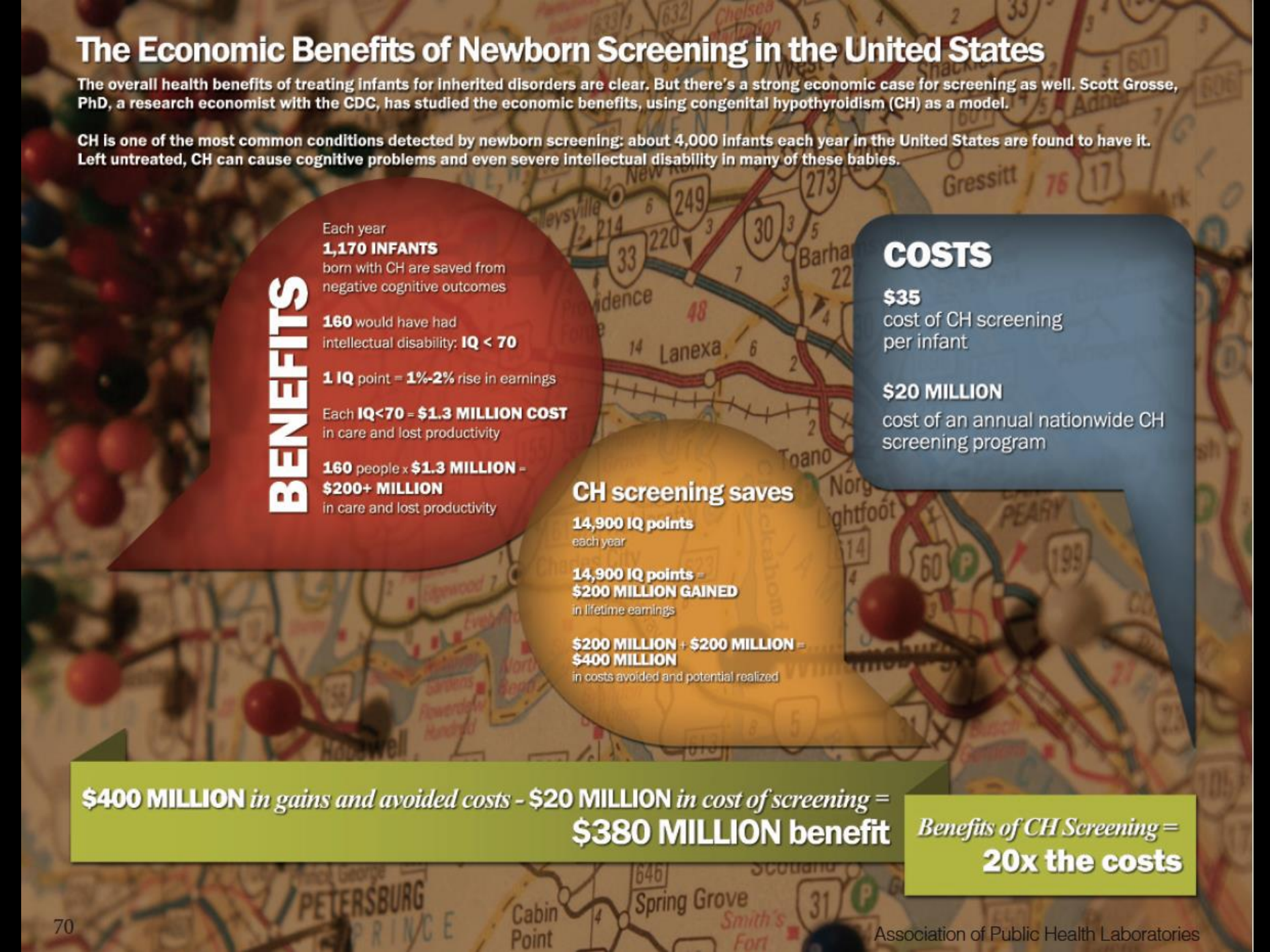
The CDC Recognizes Newborn Screening in the "Ten Great Public Health Achievements”

The American College of Medical Genetics estimates that about **12,000** of the **4.2 million** babies born each year in the United States will be identified with one of the conditions for which early intervention will have a significant impact on the child's life and long-term health."

The Economic Benefits of Newborn Screening in the United States

The overall health benefits of treating infants for inherited disorders are clear. But there's a strong economic case for screening as well. Scott Grosse, PhD, a research economist with the CDC, has studied the economic benefits, using congenital hypothyroidism (CH) as a model.

CH is one of the most common conditions detected by newborn screening: about 4,000 infants each year in the United States are found to have it. Left untreated, CH can cause cognitive problems and even severe intellectual disability in many of these babies.



If undiagnosed and untreated, these disorders can cause irreversible mental retardation (ranging from mild to severe), physical disability, neurological damage and even fatality.

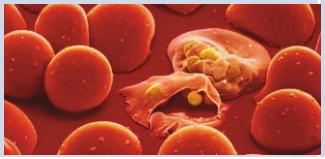
Medical Foods: Annual costs range from $2,254 for an infant to almost $25,000 for an adult male or pregnant woman.

POSITIVE SELECTION IN THE HUMAN GENOME

Correlation coefficients of allele frequencies at specific gene variants with economic-cultural type

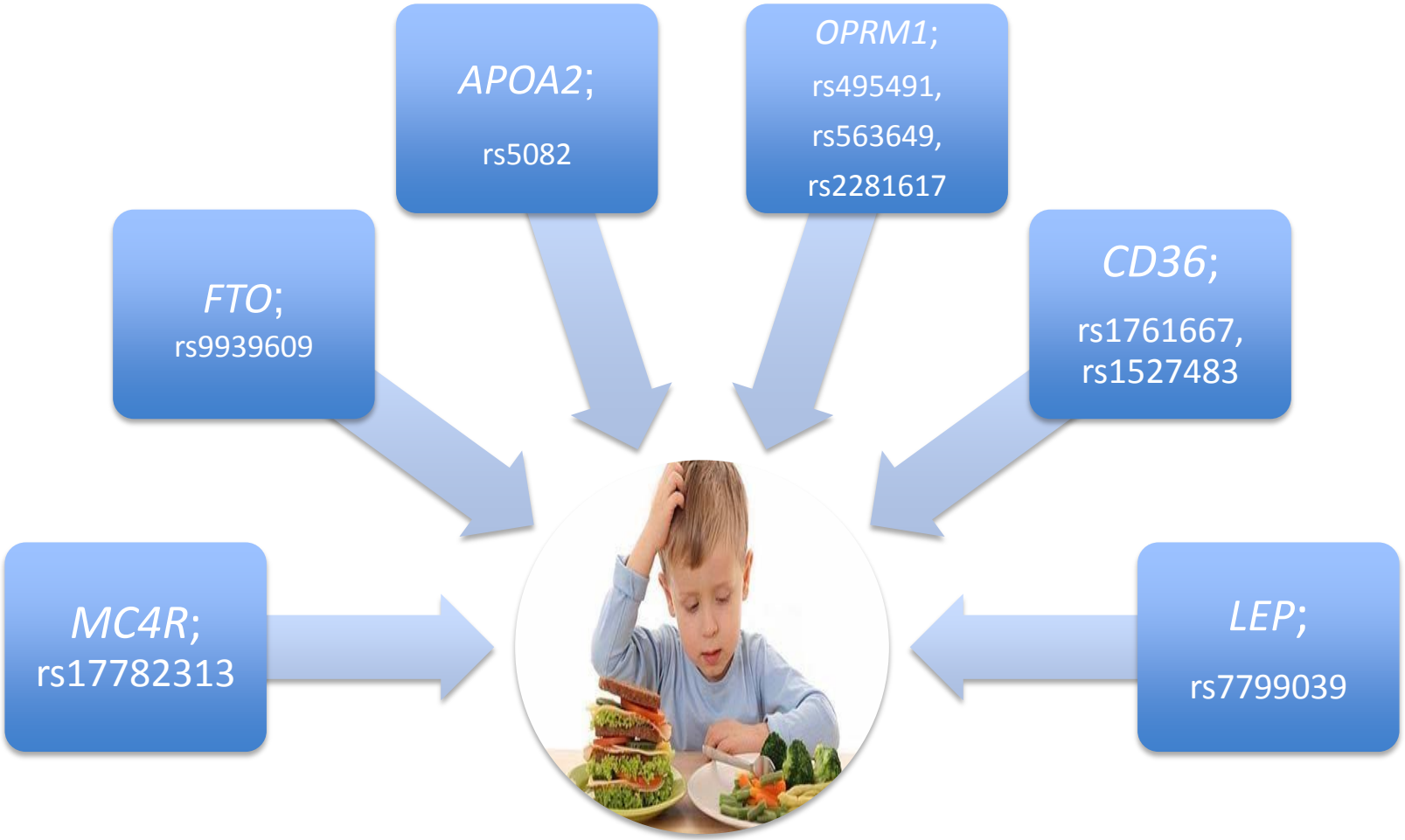
	LCT - 13910T	APOE e4	ADH1B 48His
		R= 0.557 P= 0.000	
		R=-0.327 P= 0.007	
	R= 0.463 P= 0.003		R=-0.376 P= 0.006

Correlation coefficients of allele frequencies at specific gene variants with pathogen load

	G6PD	ADH1B 48His
Malaria 	R= 0.520 P= 0.000	
Schistosomiasis 	R= 0.524 P= 0.000	
Filariasis 	R= 0.452 P= 0.000	R= 0.821 P= 0.001

Nutrition-related economic/cultural environment and Pathogens had a significant influence over the shaping and evolution of the human genome

Why some like it fatty (or not)?



Chmurzynska A and Mlodzik MA. Nutrition Research Reviews (2017), 30, 106–117

General characteristics of the study population.[a]

	Men	Women
n	514	564
Age, years	49.1 (16.1)	48.1 (16.3)
Weight, kg[b]	90.5 (16.4)	75.9 (17.1)
Height, m[b]	1.78 (0.72)	1.65 (0.68)
BMI, kg/m^2	28.5 (4.9)	28.0 (6.2)
Waist circumference, m[b]	1.00 (0.14)	0.92 (0.75)
Hip circumference, m[b]	1.05 (0.09)	1.08 (0.14)
Cholesterol, mmol/L	4.91 (0.97)	4.96 (1.04)
LDL cholesterol, mmol/L[b]	3.19 (0.79)	3.10 (0.83)
HDL cholesterol, mmol/L[b]	1.08 (0.25)	1.35 (0.36)
Triglycerides, mmol/L[b]	1.70 (1.25)	1.41 (0.93)
VLDL size, nm	51.25 (7.32)	51.17 (7.50)
LDL size, nm[b]	20.48 (0.78)	21.10 (0.87)
HDL size, nm[b]	8.65 (0.38)	9.02 (0.44)
Fasting glucose, mmol/L[b]	5.84 (1.10)	5.43 (0.88)
Energy intake, KJ/day[b]	9994 (3858)	7261 (2684)
Total fat, g/day[b]	97.2 (43.5)	68.1 (30.4)
SATFAT, g/day[b]	33.0 (15.9)	22.6 (10.8)
MUFA, g/day[b]	36.9 (16.8)	25.3 (11.5)
PUFA, g/day[b]	19.9 (9.5)	15.2 (7.3)
Proteins, g/day[b]	94.4 (39.9)	68.1 (26.6)
Carbohydrates, g/day[b]	279.8 (112.9)	218.4 (87.6)
Current smokers, n (%)	39 (7.6)	42 (7.5)
Past smokers, n (%)[a]	135 (26.3)	100 (17.8)
Current drinkers, n (%)	254 (49.4)	291 (51.6)
Diabetes or high blood sugar, n (%)	34 (6.6)	52 (9.2)
Heart attack, n (%)[b]	25 (4.7)	5 (0.9)
Stroke, n (%)	5 (1.0)	3 (0.5)
Obesity, n (%)	167 (32.5)	192 (34.0)
APOA2 −265T>C polymorphism, n (%)		
TT	188 (36.6)	213 (37.8)
TC	251 (48.8)	261 (46.3)
CC	75 (14.6)	90 (16.0)

[a] Data are mean (SD) except where noted.
[b] Statistically significant differences between men and women.

Genotype-Phenotype Associations: APOA2 m265T>C, caloric intake and BMI

TT+TC

8456 (413) kcal

29.9 (1.1) kg/m^2

87.9 (3.3) kg

CC

9371 (497) kcal

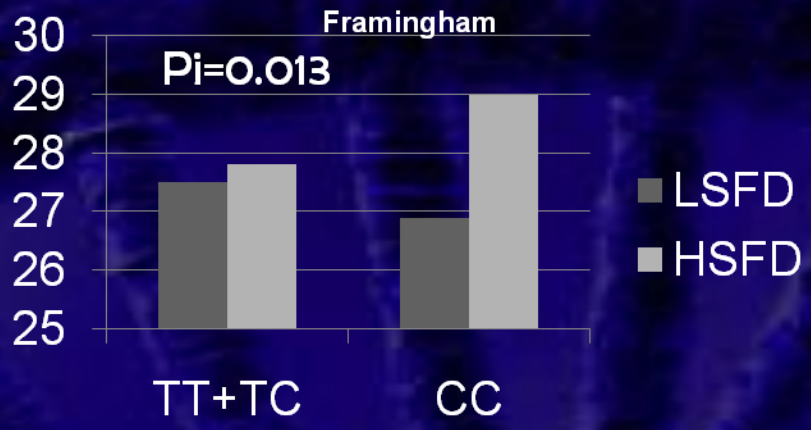
30.9 (1.2) kg/m^2

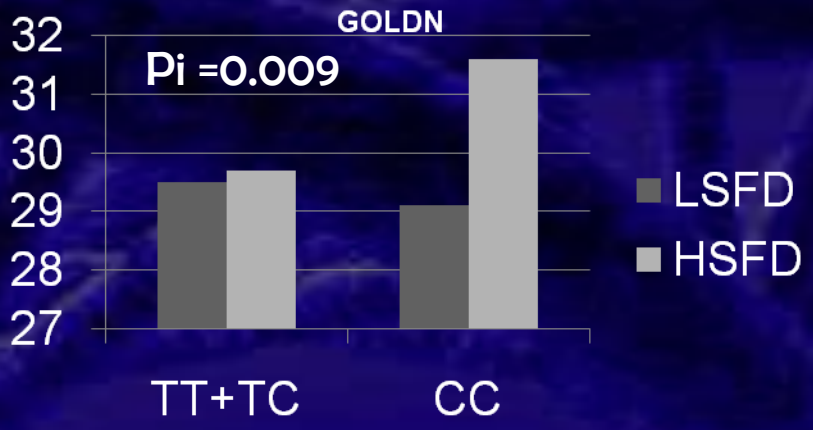
92.1 (3.5) kg

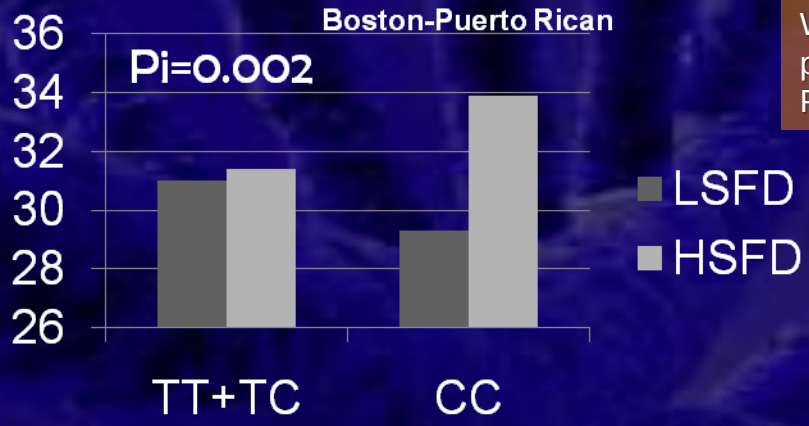
Estimated means and p values were adjusted for sex, tobacco smoking, alcohol consumption, diabetes, and CVD

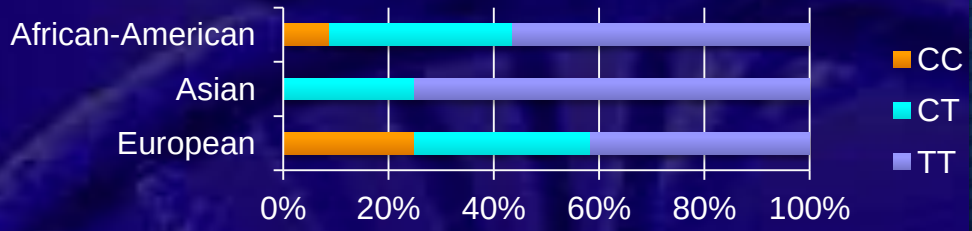
Corella D, et al. Clin Chem. 2007;53:1144-52;

GENOTYPE-PHENOTYPE ASSOCIATIONS AND INTERACTIONS: APOA2 M265T>C, SATURATED FAT AND BMI





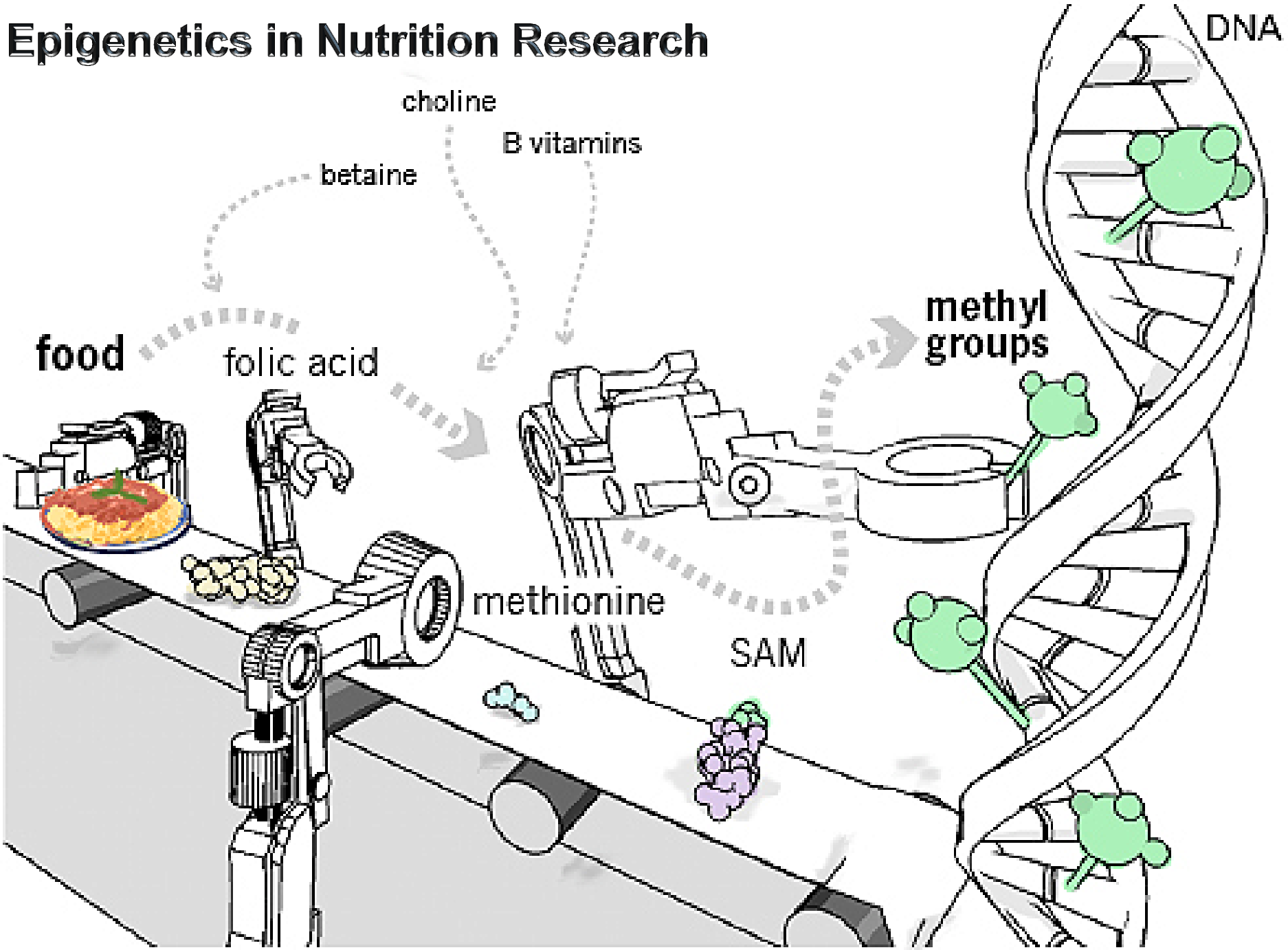


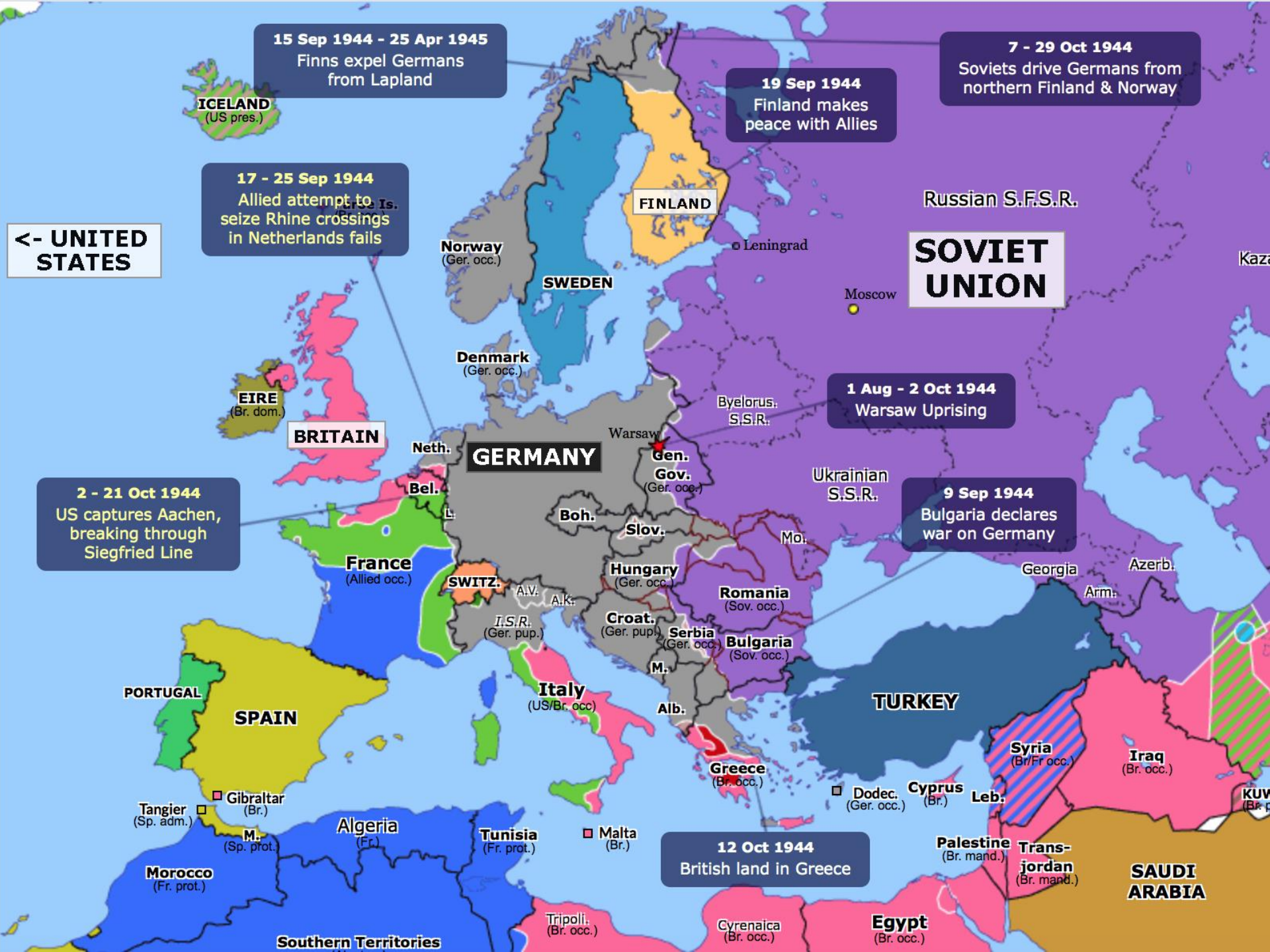


We have replicated a gene-dietary fat interaction between a functional promoter SNP at the APOA2 locus and BMI in 6 independent Populations and 5 ethnicities across the World

Smith CE et al. Int J Obes. 2011 Mar 8.; Corella D et al. Int J Obes. 2010 Oct 26.; Corella D, et al. Arch Intern Med. 2009;169:1897-906; Corella D, et al. Clin Chem. 2007;53:1144-52; Delgado-Lista J et al. J Nutr. 2007;137:2024-8

Epigenetics in Nutrition Research

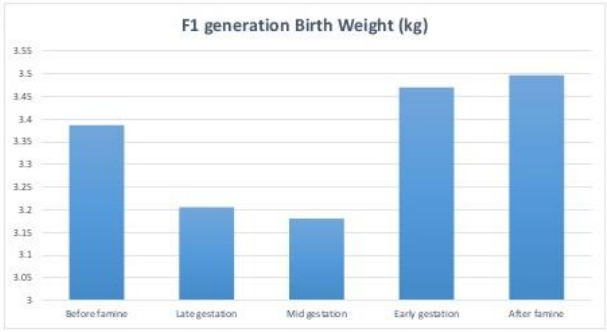


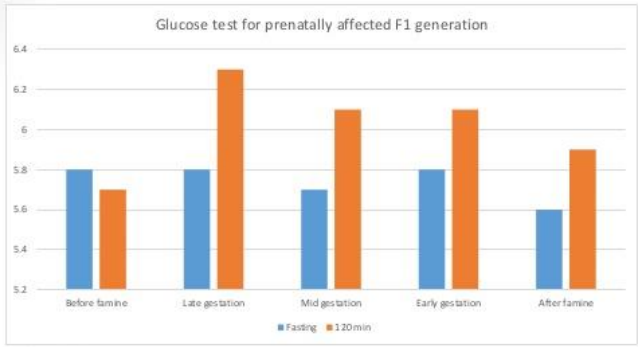

15 Sep 1944 - 25 Apr 1945
Finns expel Germans from Lapland
7 - 29 Oct 1944
Soviets drive Germans from northern Finland & Norway
19 Sep 1944
Finland makes peace with Allies
17 - 25 Sep 1944
Allied attempt to seize Rhine crossings in Netherlands fails
<- UNITED STATES
ICELAND
(US pres.)
FINLAND
Russian S.F.S.R.
SOVIET UNION
Leningrad
Moscow
Norway
(Ger. occ.)
SWEDEN
Denmark
(Ger. occ.)
EIRE
(Br. dom.)
BRITAIN
1 Aug - 2 Oct 1944
Warsaw Uprising
Byelorus. S.S.R.
Warsaw
Neth.
GERMANY
Gen. Gov.
(Ger. occ.)
Ukrainian S.S.R.
9 Sep 1944
Bulgaria declares war on Germany
2 - 21 Oct 1944
US captures Aachen, breaking through Siegfried Line
Bel.
Boh.
Slov.
Mol.
France
(Allied occ.)
SWITZ.
Hungary
(Ger. occ.)
Romania
(Sov. occ.)
Georgia
Azerb.
Arm.
A.V.
A.K.
I.S.R.
(Ger. pup.)
Croat.
(Ger. pup.)
Serbia
(Ger. occ.)
Bulgaria
(Sov. occ.)
M.
Italy
(US/Br. occ)
PORTUGAL
SPAIN
Alb.
TURKEY
Syria
(Br/Fr occ.)
Iraq
(Br. occ.)
Greece
(Br. occ.)
Gibraltar
(Br.)
Tangier
(Sp. adm.)
Dodec.
(Ger. occ.)
Cyprus
(Br.)
Leb.
Algeria
(Fr.)
Tunisia
(Fr. prot.)
Malta
(Br.)
M.
(Sp. prot.)
12 Oct 1944
British land in Greece
Palestine
(Br. mand.)
Trans-jordan
(Br. mand.)
SAUDI ARABIA
Morocco
(Fr. prot.)
Tripoli.
(Br. occ.)
Cyrenaica
(Br. occ.)
Egypt
(Br. occ.)
Southern Territories

The Dutch Famine of 1944-45 (a.k.a. "Dutch Hunger Winter")

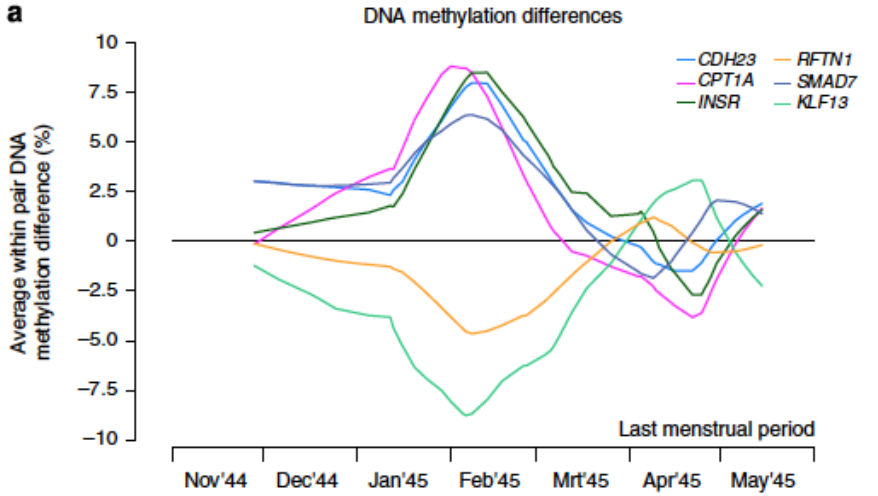
- Germany occupied parts of the Netherlands and prohibited food transport in Nov. 1944 until May 1945.
- Adult rations were as low as 400-800 calories/day
- 4.5 million people affected and the number of deaths have been estimated in 22,000.

- F1 offspring affected during mid-gestation (May-Sept 1945) and late gestation (Feb-June 1945) had low birth weight. F1 offspring affected during early gestation had normal birth weight (Rooji, 2006)
- F1 adults exposed to famine had impaired glucose tolerance and developed insulin resistance. This was more prominent in F1 exposed during mid and late gestation. This increased their risk of developing type 2 diabetes. (Ravelli, 1988)

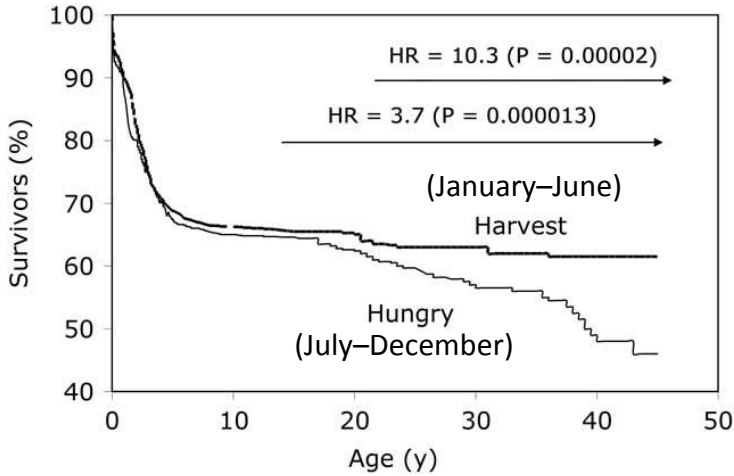


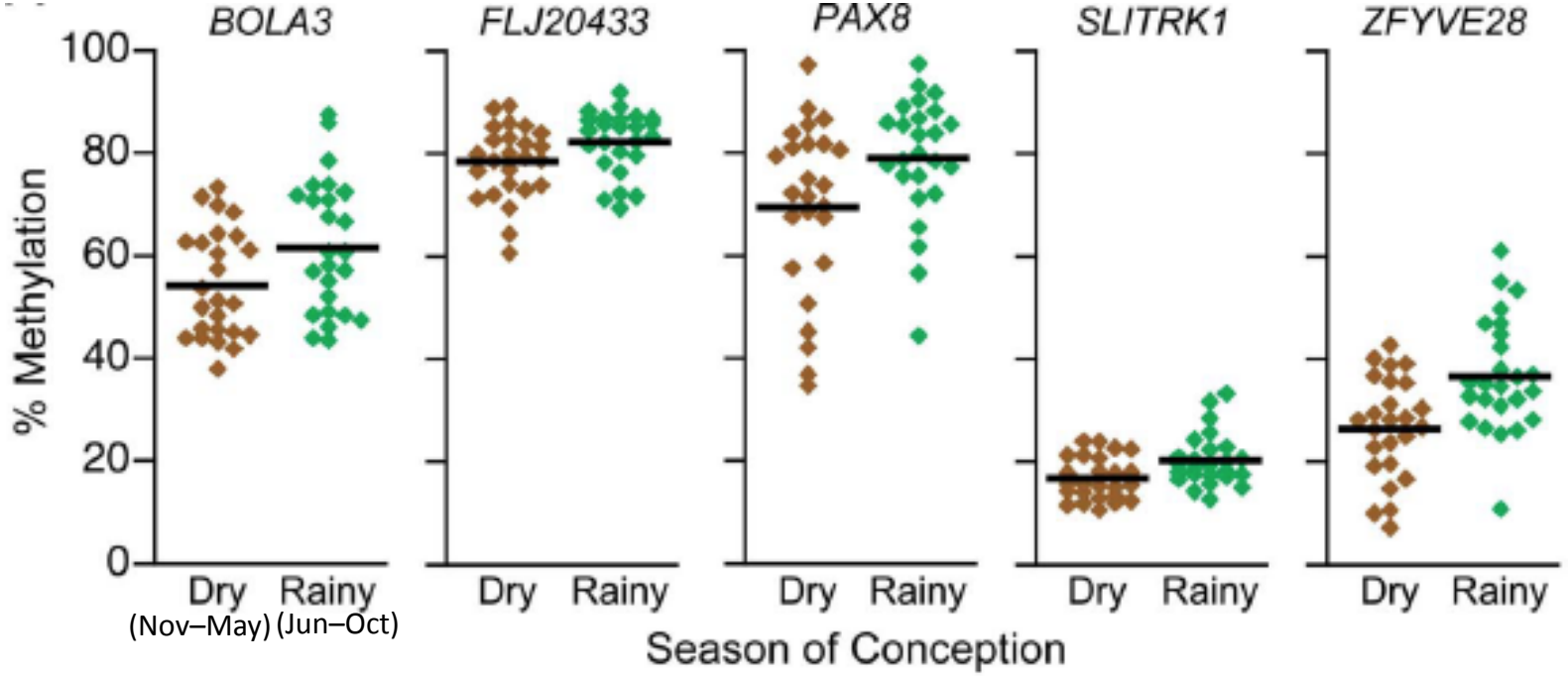


A lowess curve depicting the average within-pair difference (y axis) stratified by the estimate of the start of pregnancy (LMP; x axis). Each coloured line represents an individual prenatal malnutrition-associated differentially methylated regions (P-DMRs) (Tobi, 2014)



Season of Conception in Rural Gambia Affects DNA Methylation at Putative Human Metastable Epialleles





Waterland RA, et al. (2010) PLoS Genet 6(12): e1001252.

Whole Fruit Vs. Fruit Juice

Whole fruits vs. Fruit Juices

- Rich in fiber
- Low energy
- Vitamins and minerals are intact

- Deficient in fiber
- High energy (added sugar)
- Most of the vitamins and minerals are lost

Fruit and Juice Epigenetic Signatures Are Associated with Independent Immunoregulatory Pathways

Nicodemus-Johnson J, Sinnott RA. Nutrients. 2017 Jul 14;9(7). pii: E752.

Fruit and Juice Epigenetic Signatures Are Associated with Independent Immunoregulatory Pathways

The fruit-specific epigenetic signature was enriched for only adaptive immune system genes, as well as those involved in cell cycle regulation and chromosome or telomere maintenance.

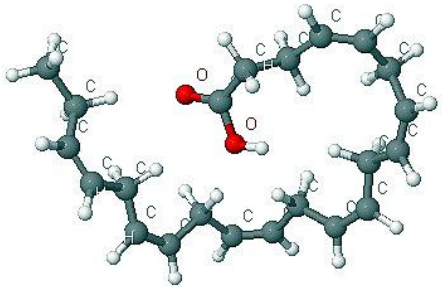
B

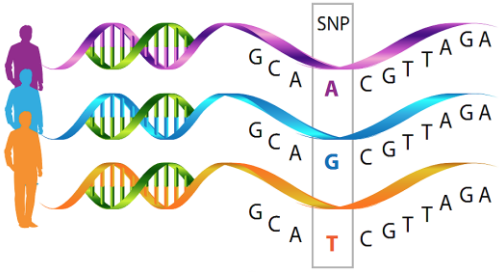
The juice-specific epigenetic signature was enriched for innate and adaptive immune system genes,

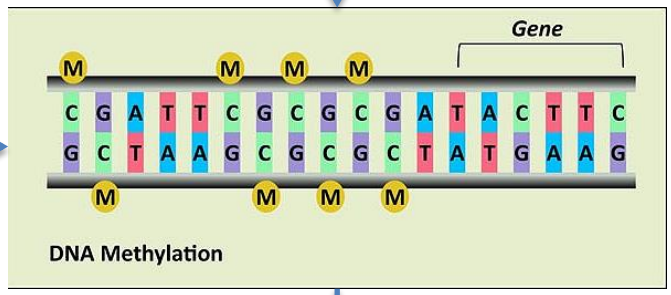
Nicodemus-Johnson J, Sinnott RA. Nutrients. 2017 Jul 14;9(7). pii: E752.

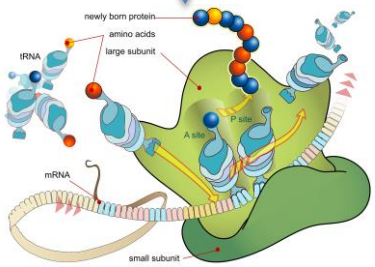
The integration of Genetics and Epigenetics in Nutrition Research

Epigenetics Meets Genetics (and Nutrition)









- We found that over 80% of genetic variants at CpG sites (meSNPs) are meQTL loci (P value < 10^{-9}), and meSNPs account for over two thirds of the strongest meQTL signals (P value < 10^{-200}).

- Beyond direct effects on the methylation of the meSNP site, the CpG-disrupting allele of meSNPs were associated with lowered methylation of CpG sites located within 45 bp. The effect of meSNPs extends to as far as 10 kb and can contribute to the observed meQTL signals in the surrounding region, likely through correlated methylation patterns and linkage disequilibrium.

- Therefore, meSNPs are behind a large portion of observed meQTL signals and play a crucial role in the biological process linking genetic variation to epigenetic changes.

LIPID PROFILE

	DESIRABLE	BORDERLINE	HIGH RISK
Cholesterol	<200 mg/dl	200-239 mg/dl	240 mg/dl
Triglycerides	<150 mg/dl	150-199 mg/dl	200-499 mg/dl
HDL cholesterol	60 mg/dl	35-45 mg/dl	<35 mg/dl
LDL cholesterol	60-130 mg/dl	130-159 mg/dl	160-189 mg/dl
Cholesterol/ HDL ratio	4.0	5.0	6.0

Zhi D. et al. Epigenetics. 2013 Aug;8(8):802-6.

CHS

InCHIANTI
INVECCHIARE NEL CHIANTI

ARIC

GOLDN

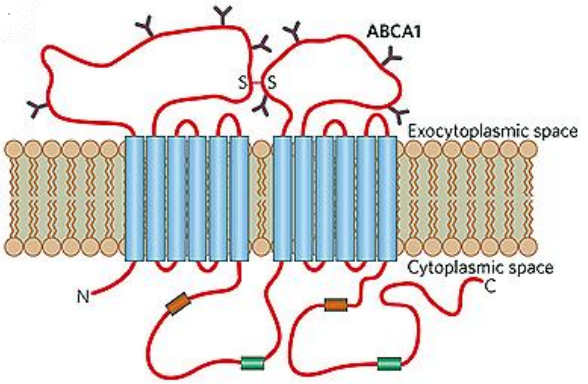
MESA

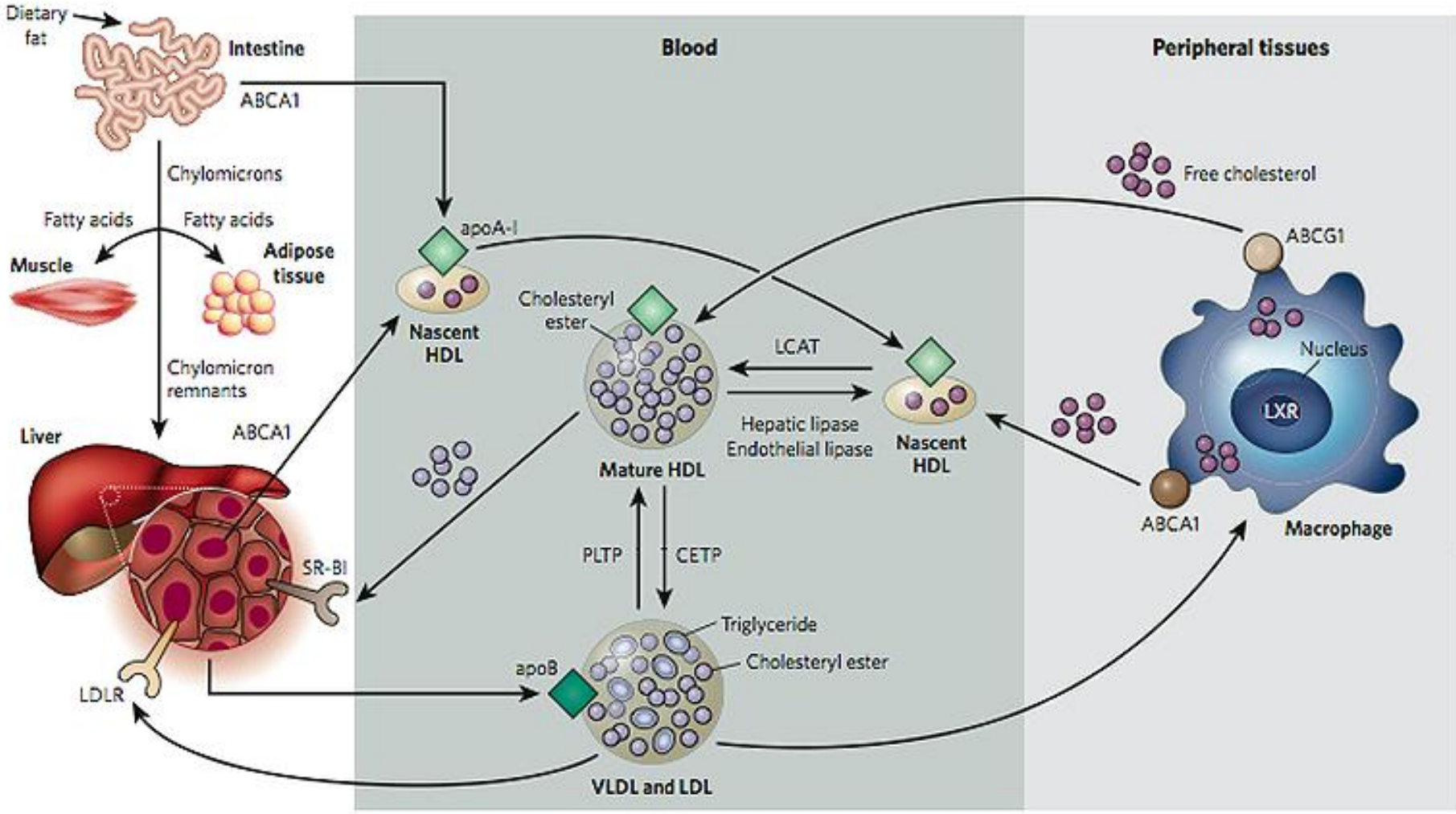
n=10,472

ENCODE

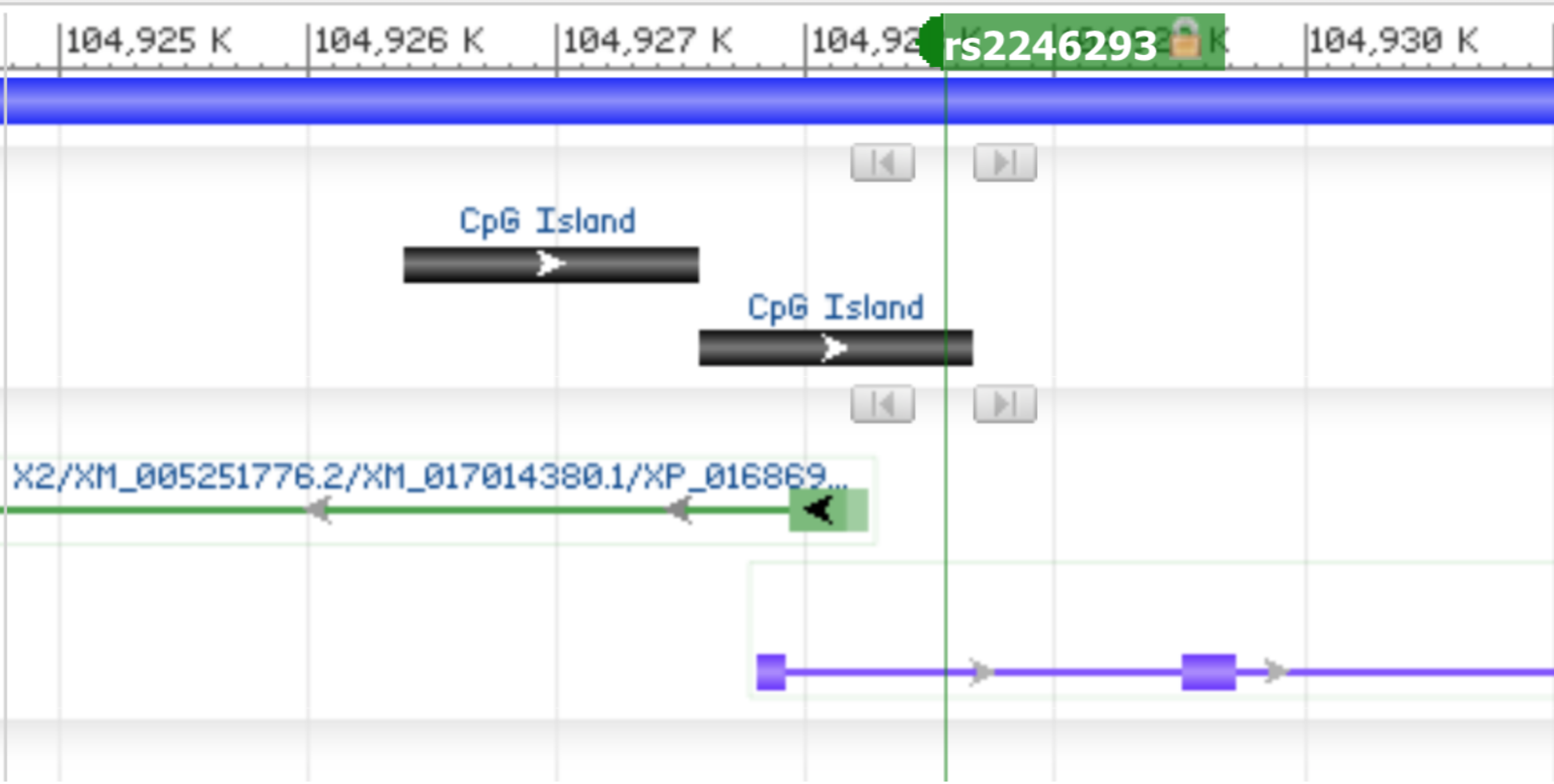
Harvard Medical School
Brigham and Women's Hospital
Women's Health Study

ABCA1 and HDL Metabolism/Cholesterol Efflux





ATP binding cassette subfamily A member 1 (*ABCA1*) rs2246293 SNP, cg14019050 CpG, circulating EPA and plasma HDLC levels



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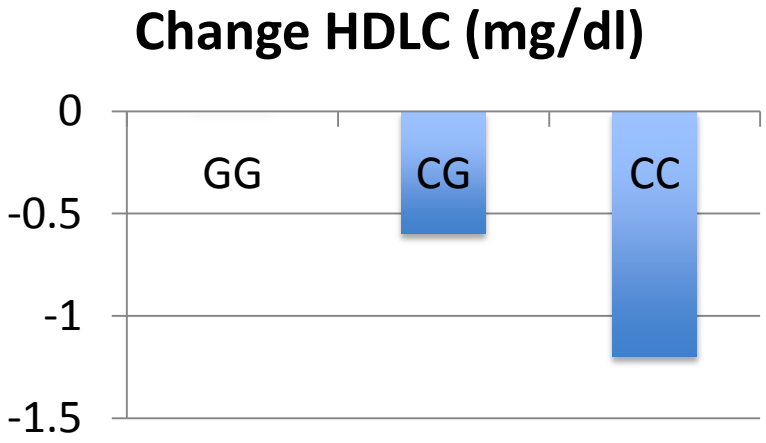
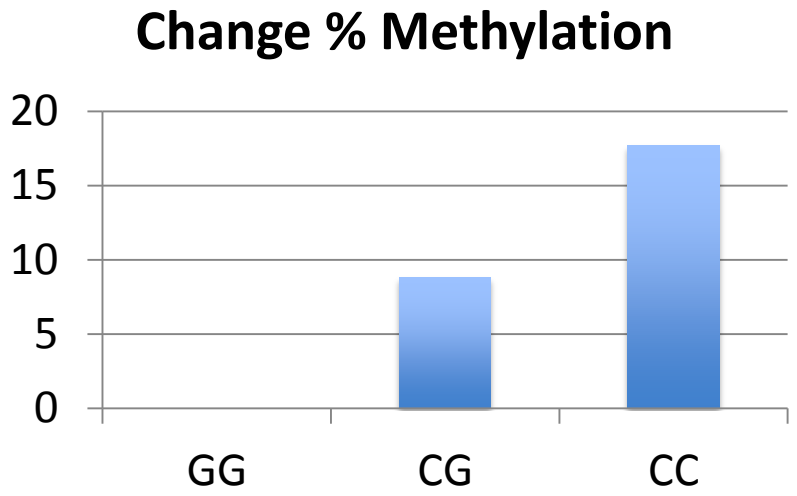
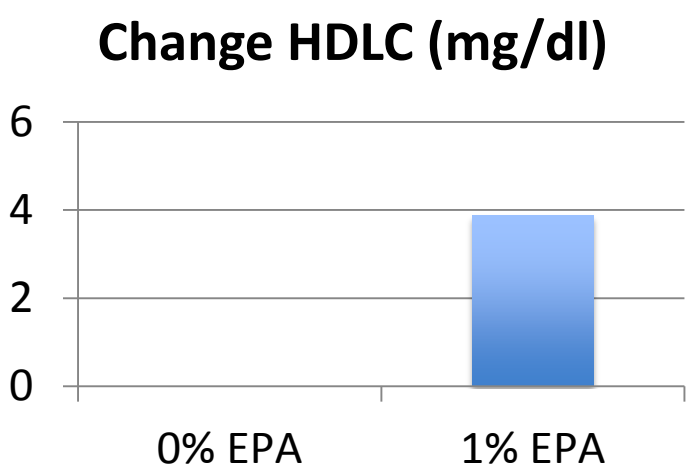
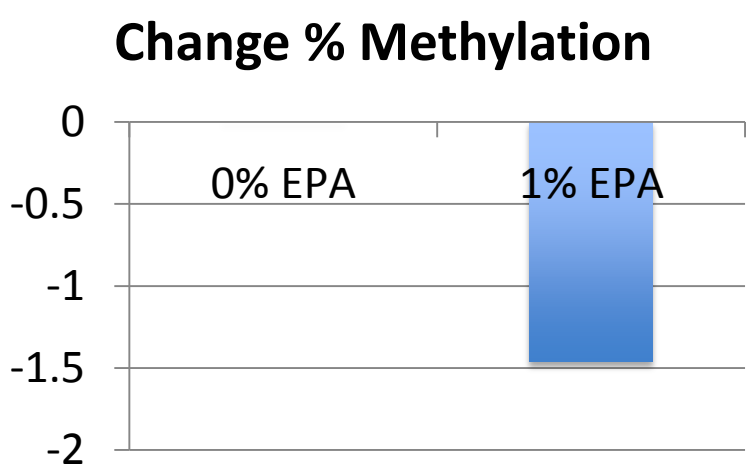


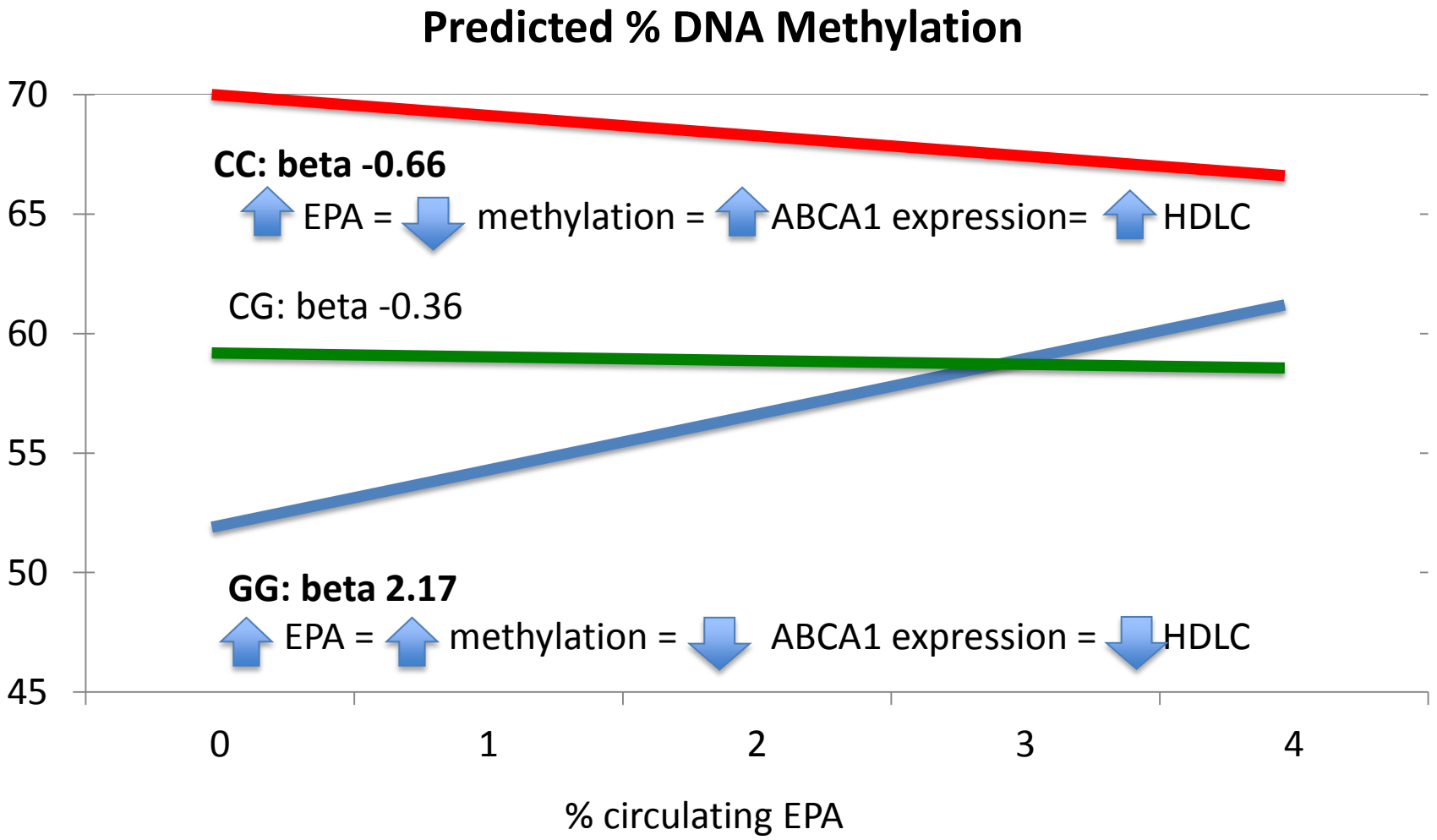






Ma Y, et al. Am J Clin Nutr. 2016; Feb;103(2):567-78.

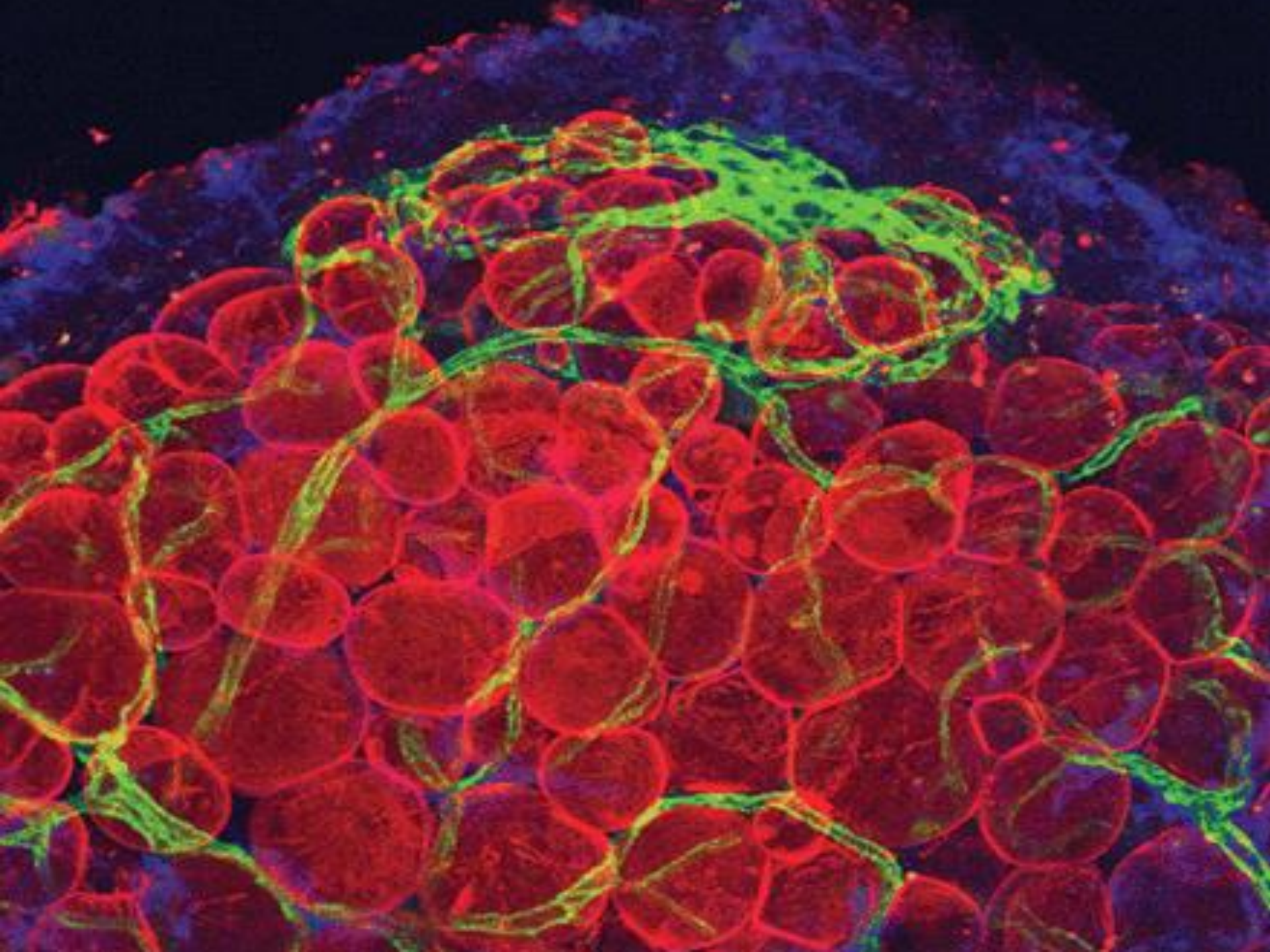
ATP binding cassette subfamily A member 1 (*ABCA1*) rs2246293 SNP, cg14019050 CpG, circulating EPA and plasma HDLC levels



Ma Y, et al. Am J Clin Nutr. 2016; Feb;103(2):567-78.

Summary

EPA decreases ABCA1 promoter methylation, which leads to an increase in the gene expression of ABCA1 and a corresponding increase in plasma HDL cholesterol and this proposed sequence of events may be genotype-dependent.



Associations of PLIN4 rs8887 SNP in the FOS and GOLDN populations with Anthropometric traits - Main Effects

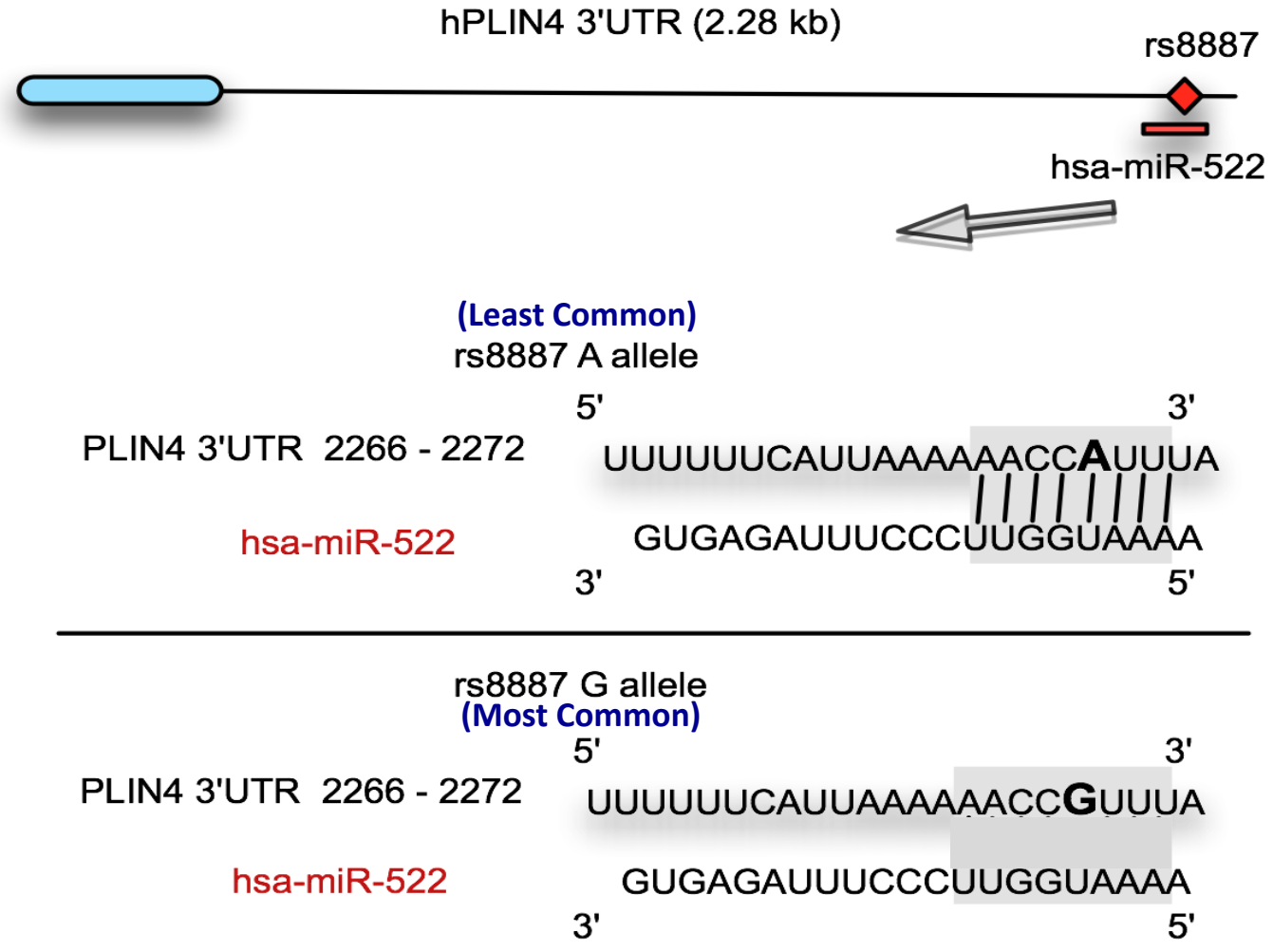
			FOS				GOLDN				Meta-Analysis	
SNP	Phenotype	Gender	Beta	Se	P	%Var	Beta	Se	P	%Var	z-score	P
rs8887	BMI	Both	0.614	0.221	0.005	0.396	.581	0.378	0.125	0.334	3.164	0.002
		Males	0.624	0.269	0.021		0.326	0.461	0.480		2.319	0.020
		Females	0.631	0.335	.060		0.704	0.586	0.230		2.231	0.026
	Weight	Both	3.106	1.431	0.030	0.200	2.374	2.271	0.296	0.081	2.387	0.017
		Males	2.917	1.980	0.141		0.584	3.146	0.853		1.332	0.183
		Females	3.524	2.010	0.080		3.465	3.242	0.286		2.050	0.040
	Waist	Both	0.423	0.221	0.056	0.157	0.252	0.440	0.567	0.023	1.911	0.056
		Males	0.483	0.269	0.073		−0.085	0.565	0.880		1.413	0.158
		Females	0.381	0.334	0.253		0.397	0.656	0.556		1.278	0.201
	VAT	Both	199.5	67.55	0.003							
		Males	345.4	100.5	0.001							
		Females	68.7	83.97	0.413							
	SAT	Both	229.1	90.66	0.011							
		Males	180.4	106.2	0.090							
		Females	248.9	147.2	0.054							

Men
FOS (N = 1259) GOLDN (N = 481)
Women
FOS (N = 1352) G0LDN (N = 513)

We can only speculate how lower expression of PLIN4 contributes to obesity-related phenotypes. For the related PLIN1, one study demonstrated that obesity and high lipolysis rates are independently associated with lower PLIN1 protein levels in women, whereas another demonstrated reduced levels of both PLIN1 mRNA and protein in obese compared to non-obese subjects. Conversely, the Plin1-/- mouse is characterized by a lean phenotype. These data suggest the role and regulation of the PAT gene family in human obesity may be different than in model organisms.

Richardson K, et al. PLoS ONE 6(4): e17944. doi:10.1371/journal.pone.0017944

PERILIPIN4 (PLIN4) rs8887 SNP creates a seed site for miR-522 and it is associated with BMI



PLIN4 rs8887 SNP by diet interactions

				FOS				GOLDN				Meta-Analysis	
SNP	Phenotype	PUFA	Gender	Beta	Se	P	%Var	Beta	Se	P	%Var	z-score	P
rs8887	BMI	n3	Both	−0.469	0.391	0.230	0.48	−1.208	0.459	0.009	0.77	−2.447	0.014
			Males	−0.624	0.466	0.181		−1.158	0.542	0.033		−2.288	0.022
			Females	−0.438	0.625	0.484		−0.964	0.838	0.251		−1.216	0.224
	Weight	n3	Both	−3.867	2.522	0.125	0.30	−7.189		0.009	0.44	−2.707	0.007
			Males	−3.778	3.430	0.271		−7.080		0.057		−1.964	0.049
			Females	−4.553	3.750	0.225		−6.046		0.194		−1.728	0.084
	Waist	n3	Both	−0.461	0.391	0.238	0.23	−1.444	0.544	0.008	0.55	−2.445	0.015
			Males	−0.500	0.466	0.283		−1.230	0.672	0.068		−1.900	0.057
			Females	−0.421	0.621	0.498		−1.584	0.952	0.097		−1.483	0.138

A

G-like

Our data indicate for rs8887 minor allele carriers that elevated intake of PUFA n3 results in decreasing anthropometrics compared to non-carriers. Due to what little is known of PLIN4 regulation, it is difficult to propose a mechanism by which the miR-522 rs8887 interaction together with PUFA n3 could modulate anthropometrics. It is likely that PUFA n3 alters PLIN4 expression through PPAR mediated pathways

Personalized Nutrition

Moderate carb, high protein, low fat diet

Low fructose diet

Gluten free diet

Low starch diet

Low protein, low carb diet

High fat diet

Low glycemic index diet

High protein, low carb diet

High starch diet

Ketogenic diet

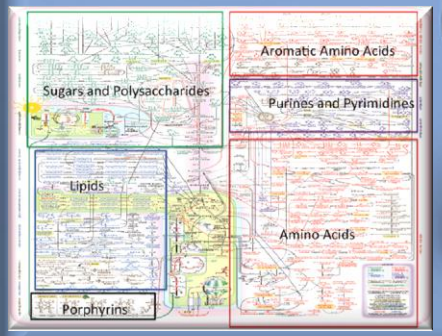
Low fat diet

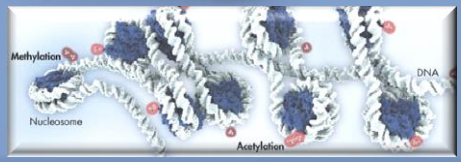
High fat, moderate carb, low protein diet

High carb diet

Low protein diet

Vegan diet





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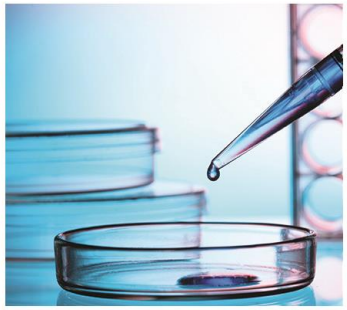
HNRCA



Jose M Ordovas

Genotypes and Disease Risk: What Do We Currently Know about Nutrition and Epigenetics?

Thank you

Tufts UNIVERSITY