SESSION 2: NUTRITIONAL AND DIETARY GENETICS

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AnantLife

REVIEW FROM LECTURE 1

- 3 living domains
- Cell types
- Organization of DNA in cells
- Genome, Gene, Allele
- Nucleotides
- **Difference between RNA and DNA**
- **Types of RNA**
- **Replication**
- **Transcription**
- Translation
- Epigenetics & DNA methylation
- **Mutation, mutation types and examples**
- **Genetic testing, types of genetic testing**
- **Methods for DNA analysis**
- **Methods comparatives**
- **Bioinformatics**

SESSIONS 1 - 8

Session	Topic	Evaluations
1	INTRODUCTION TO MOLECULAR GENETICS, MOLECULAR BIOLOGY AND HUMAN GENETICS	Discussion – Participation
2	**NUTRITIONAL AND DIETARY GENETICS: HOW DO OUR GENES REGULATE OUR NUTRITION AND NUTRITIONAL HEALTH?**	**Discussion - Participation**
3.	FITNESS GENETICS AND GENETICS OF CHRONIC DISEASES: HOW DO OUR GENES REGULATE OUR RESPONSE TO EXERCISE AND HOW DO GENES REGULATE THE RISK OF CHRONIC METABOLIC DISORDERS?	Discussion - Participation
4.	DETOXIFICATION GENETICS: HOW DO OUR GENES REGULATE DETOXIFICATION WHICH INDIRECTLY IMPACTS OVERALL HEALTH AND DISEASE RISK?	Discussion - Participation
5.	NEUROGENETICS: HOW DO OUR GENES REGULATE THE SYNTHESIS AND BREAKDOWN OF NEUROTRANSMITTERS AND ITS IMPACT ON OUR HEALTH ?	Take home exam on sections 1-5, due during session 6
6.	GENETICS OF ENDOCANNABINOID PATHWAYS: HOW DO OUR GENES REGULATE THE RESPONSE TO CANNABIS?	Discussion - Participation
7.	SKIN GENETICS: HOW DO OUR GENES REGULATE OUR SKIN HEALTH ?	Take home assignment – due during session 8
8.	DISCUSSION AND PRACTICAL APPLICATIONS OF GENETIC TESTS DISCUSSED IN SESSIONS 2-7	Discussion - Participation

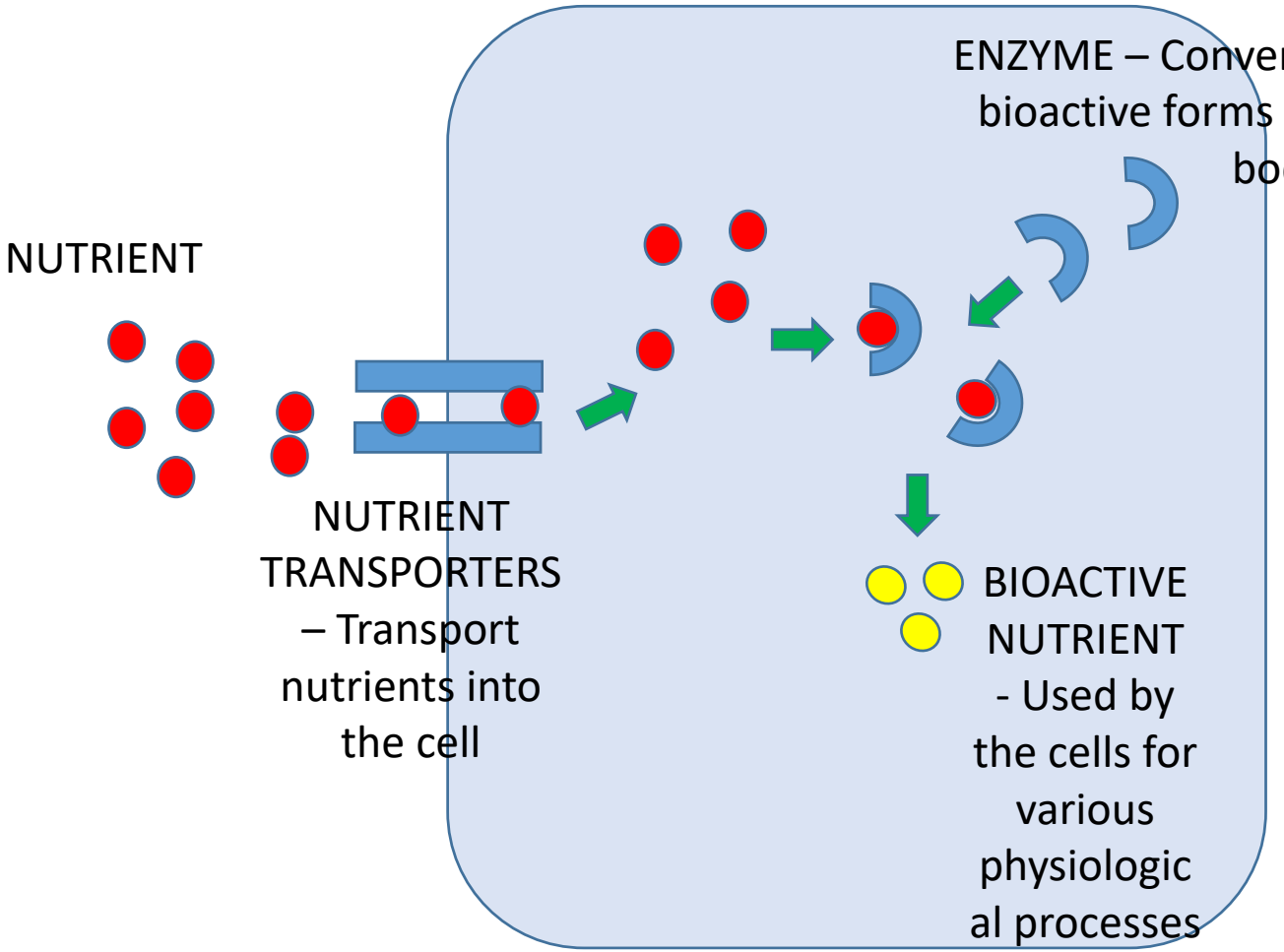
SESSION OBJECTIVES:

- How does genetics impact nutrition ?
- How does genetics impact risk of food intolerances ?
- How does genetics impact diet and diet dependent weight loss ?

NUTRIENTS WITH CLEARLY IDENTIFIED GENETIC COMPONENT FOR PREDISPOSITION RISK

Vitamin A
Vitamin B6
Vitamin B12
Choline
Vitamin C
Vitamin D
Vitamin E
Folate
Calcium
Iron (Low/overload)
Magnesium
Selenium
Zinc

NUTRIENTS ABSORPTION BY HUMAN CELLS



Enzymes, transporters are all encoded by DNA

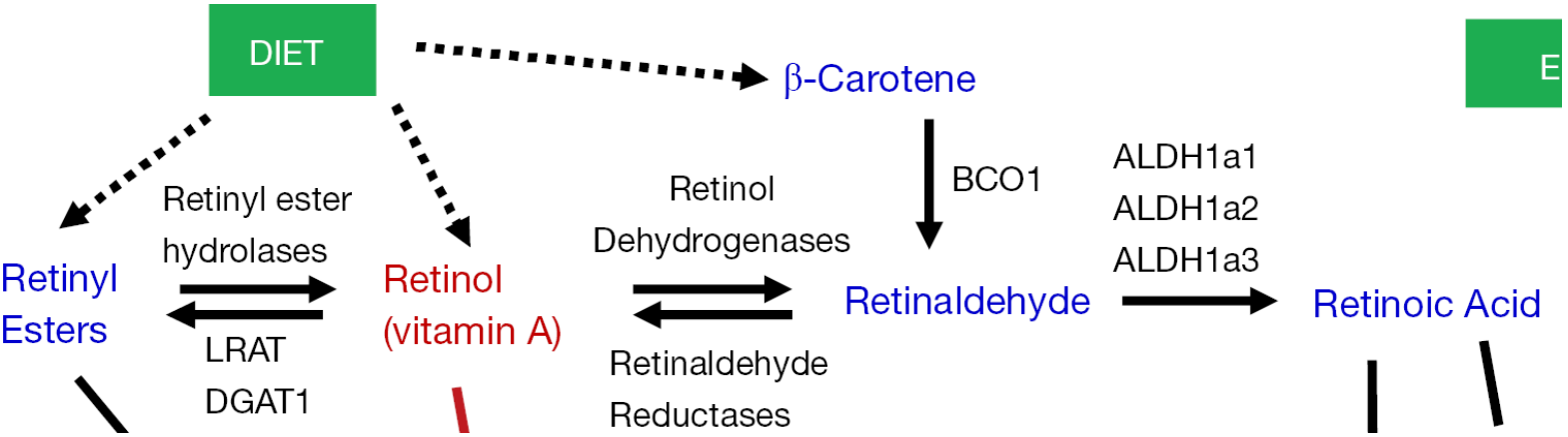
Questions:

1. **What happens if your nutrient transporters have decreased activity?**
2. **What happens if the enzyme has decreased activity**

VITAMIN A

- Growth (production of HGH, normal functioning of osteoblasts and osteoclasts)
- Reproduction
- Embryonic development (retinoic acid influences cell differentiation)
- Vision (eye uses retinal to transduce light into neural signals and retinoic acid to maintain cornea/conjuctival membrane differentiation which prevents xerophthalmia)
- Gene expression (retinioic acid regulates expression of encoding genes for structural proteins, enzymes, extracellular matrix proteins, and retinol binding proteins and receptors)
- Immune function (retinol regulates lymphocyte physiology)
- Glycoprotein synthesis

VITAMIN A AND GENETICS



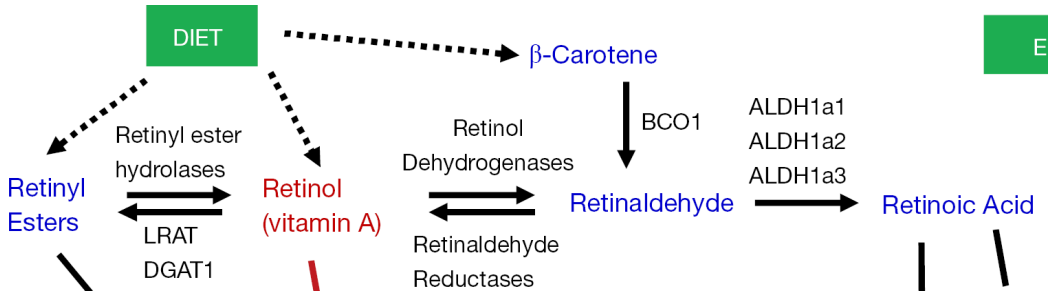
Retinol and Beta-carotene are two prominent sources of Vitamin A

Beta-carotene – plants
Retinol – Animal products

Beta carotene and Retinol are converted to Retinoic acid (Vitamin A)

BCO1 IS A KEY ENZYME INVOLVED IN CONVERSION OF BETA CAROTENE TO RETINOIC ACID

BCO1 MUTATIONS



45% of population does not respond to intake of beta-carotene to increase vitamin A levels

REASON: IMPAIRED ACTIVITY OF BCO1

T Allele variant – Reduced BCO1 activity (Upto 69% reduction in ability to convert Beta carotene into retinoic acid)

WHAT DOES THIS MEAN?

If you have the T variant of BCO-1 – Increased risk of Vitamin A deficiency and intake of beta-carotene will not alleviate the risk. Retinol rich diet needs to be explored

VITAMIN B6

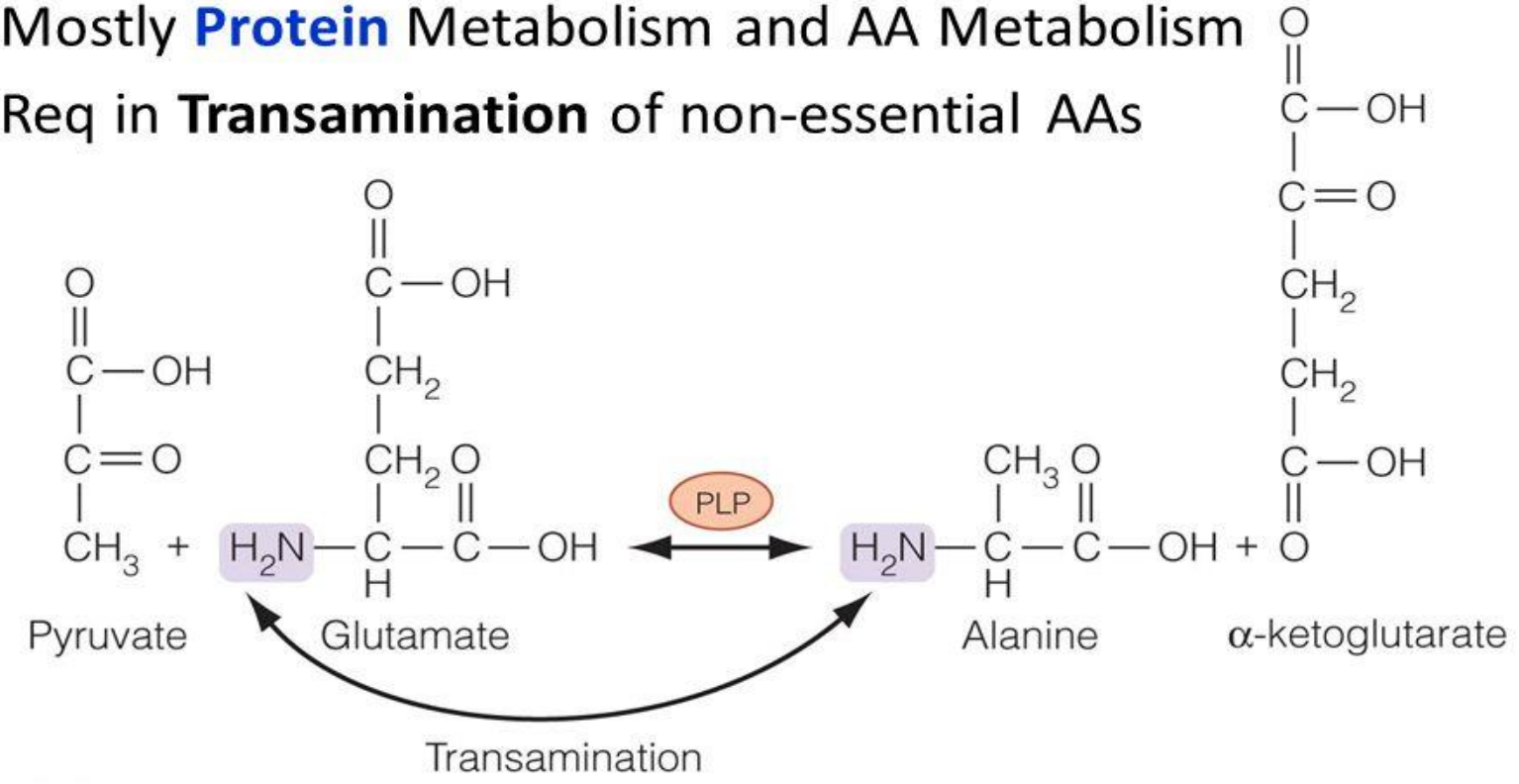
Vitamin B6

aids in

* Prevention of heart disease
  by decreasing homocysteine levels
* Maintains healthy blood vessels
* Supports brain health/function
* Improves mood
* Aids in Anemia
  by helping create hemoglobin
* Protects eye health
* Helps reduce pain and muscle spasm
* Helps manage high blood pressure
* Helps provide relief for PMS symptoms
* Regulates sleep cycles
* Prevents kidney stones
* Aids in treatment of asthma

Metabolic Functions of Vitamin B_6

- **Coenzyme** for more than 100 enzymes!
- Mostly **Protein** Metabolism and AA Metabolism
- Req in **Transamination** of non-essential AAs



NBPF3 AND VITAMIN B6 DEFICIENCY

- **Neuroblastoma Breakpoint Member 3 (NBPF3) gene is associated with the synthesis of NBPF3, a hormone found to be associated with the clearance of vitamin B6 from the body.**

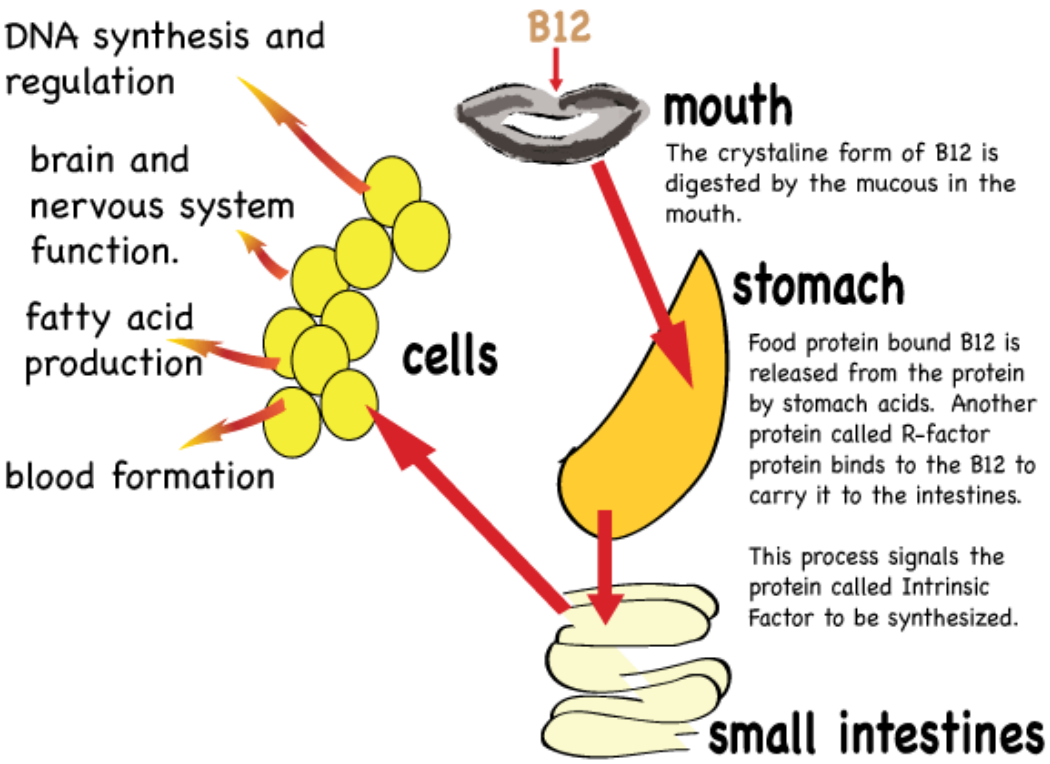
- **In a study on nearly 2800 individuals, people with the C variant of the gene were associated with lower levels of vitamin B6. There was a per allele reduction of 1. 45ng/mL- 2.90 ng/mL of vitamin B6 levels in the body.**

- **The reduction in the level of vitamin B6 among people with the C variant of the gene was shown to be associated with greater clearance of vitamin B6 from the body.**

C ALLELE CARRIERS AND DEFICIENCY

- **C allele carriers are at an increased risk of developing Vitamin B6 deficiency**
- **Homozygous CC – need higher Vitamin B6 intake than RDA to maintain adequate levels**
- **Heterozygous – Incorporate Vitamin B6 supplementation + foods rich in Vitamin B6 to ensure RDA**

VITAMIN B12 - COBALAMIN



VITAMIN B12 AND FUT2

- **FUT2 encodes for fucosyltransferase**
- **Mediates the transfer of fucose to the terminal galactose on glycan chains of cell surface glycoproteins and glycolipids. The resulting epitope plays a role in cell-cell interaction including host-microbe interaction**
- **FUT2 mutations associated with lower Vitamin B12 levels**
- **FUT2 might influence holoHC (Haptocorrin – Vitamin B12 binding protein) concentration by altering the post-translation modifications of the heavily glycosylated HC**
- **Other hypothesis also proposed but the exact mechanism is not completely understood**

CHOLINE AND PEMT

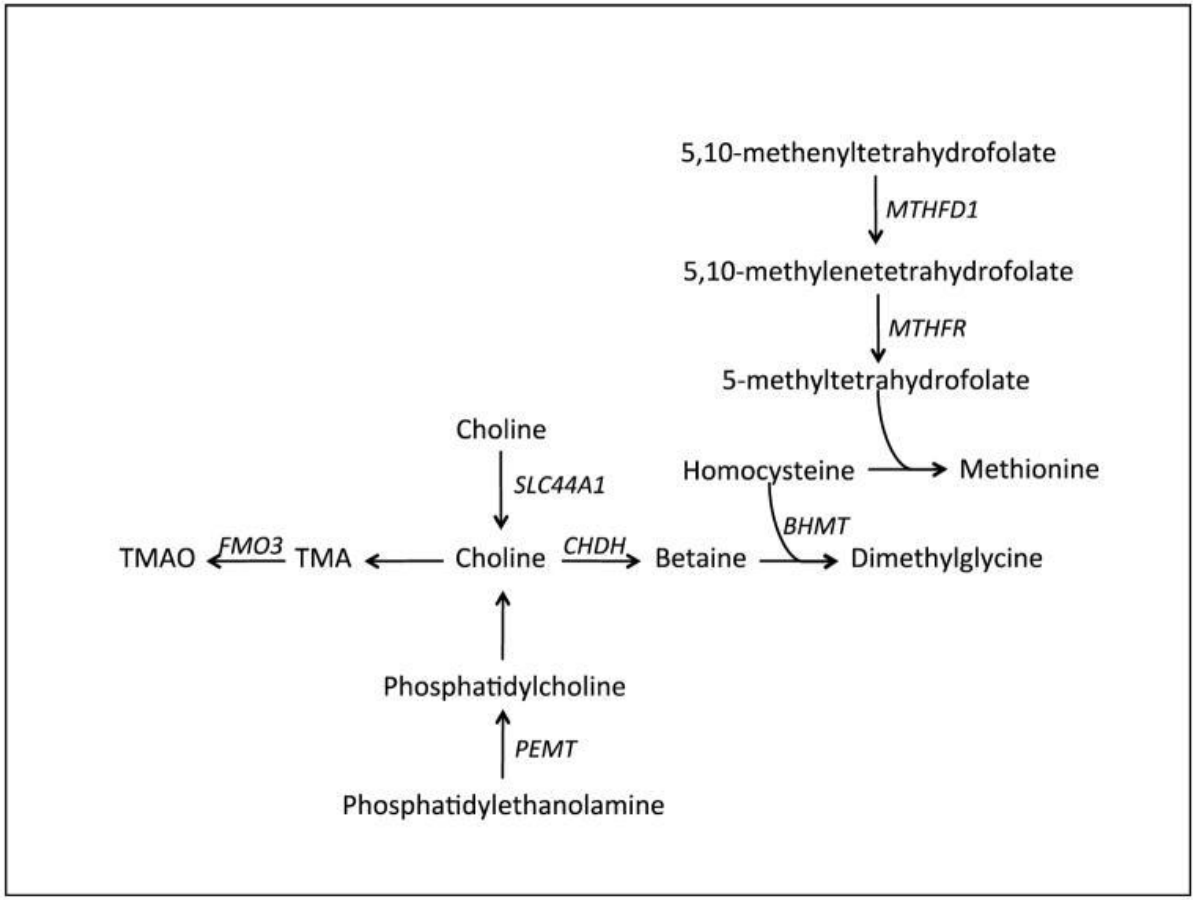
- **Choline is needed to produce acetylcholine, an important neurotransmitter for memory, mood, muscle control, and other brain and nervous system functions**

- **Choline also plays important roles in modulating gene expression, cell membrane signaling, lipid transport and metabolism, and early brain development**

- **Choline deficiency can cause muscle damage, liver damage, and non alcoholic fatty liver disease**

CHOLINE AND PEMT

- **PEMT gene is a transferase enzyme which converts phosphatidylethanolamine (PE) to phosphatidylcholine (PC) in the liver**



CHOLINE AND PEMT

TABLE 3. *Effect of PEMT promoter SNP rs12325817 (-744 G→C) on susceptibility to organ dysfunction in humans eating a low choline diet*[a]

	Signs of choline deficiency	GG	GC	CC	*P* value OR (95% CI)
All subjects (37)	Yes	7	25	7	0.10
	No	8	7	3	
Men (26)	Yes	6	10	4	0.49
	No	1	2	3	
All women (31)	Yes	1	15	3	**0.002**
	No	7	5	0	**25** (2, 256)
Pre menopausal (16)	Yes	1	4	2	0.10
	No	5	4	0	
Postmenopausal (15)	Yes	0	11	1	**0.03**
	No	2	1	0	**42** (1, 1348)[b]

[a]Subjects were fed a diet low in choline, and some developed signs of organ dysfunction (liver or muscle) that were reversed when choline was added back to their diets. Numbers of subjects are indicated for each genotype. Two-sided *P* values were calculated with a 2 × 3 Fisher exact test. For $P < 0.05$, odds ratios (OR) and 95% confidence intervals (CI) were calculated as the odds of showing signs of deficiency for subjects with the C allele divided by the odds of showing signs of deficiency for subjects without the C allele. [b]For postmenopausal and premenopausal women (where some cells were 0; see above), the odds ratio and 95% confidence intervals were computed after adding 0.5 to each cell, so these values underestimate the true values.

C allele carriers of PEMT develop organ dysfunction when fed a low choline diet – BUT THIS IS REVERSIBLE

WHAT TO DO IF SOMEONE IS CARRYING C ALLELE OF PEMT?

- Increased risk of choline deficiency
- Increased risk of organ dysfunction with low choline diet
- Dietary supplementation with choline is needed
- Estrogen causes increased production of PEMT mRNA

VITAMIN C AND SLC23A1

- **Vitamin C is an essential co-factor in multiple enzymatic pathways**
- **High levels of Vitamin C have been shown to induce cancer apoptosis**
- **Low vitamin C levels associated with poor survival of cancer patients**

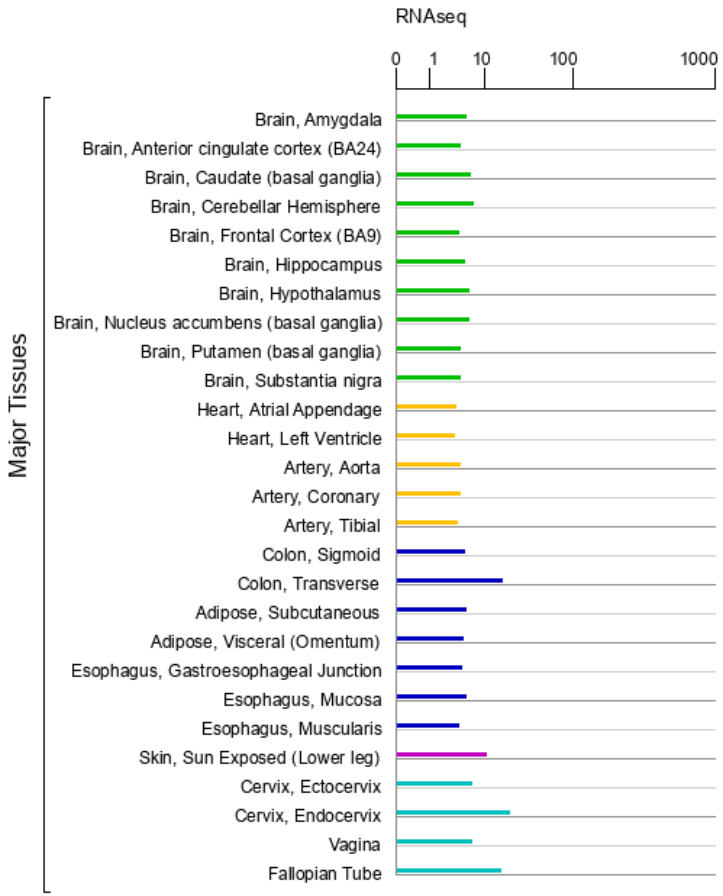
Table 2 Dietary portions, demographic and biochemical data between low and normal plasma vitamin C groups

	Mean scores (SD)		Significance
	Low plasma vitamin C*	Normal plasma vitamin C	
Survival	29 days (19)	121 days (132)	P =0.001
Age	64.4 years (7.8)	65.5 years (13.0)	Not significant
Barthel	74 (14)	79 (22)	Not significant
Dietary portions	3.2 (2.8)	6.8 (5.7)	P =0.005
Haemoglobin	11.0 (1.8)	11.6 (1.4)	Not significant
INR	1.4 (0.6)	1.1 (0.3)	Not significant
Albumin	27.3 (3.1)	33.6 (6.4)	P =0.001
Platelets	459 (155)	350 (172)	P =0.042
Urea	6.7 (3.9)	7.8 (5.9)	Not significant
CRP	105.6 (51.7)	52.0 (56.1)	P =0.003

*Low plasma vitamin C <11 μmol/L.

VITAMIN C AND SLC23A1

- **SLC23A1 is expressed in all major tissues in humans and is a Vitamin C transporter**
- **SLC23A1 mutations can cause 40-75% reduction in ascorbate transport**
- **Strongly associated with decreased plasma and serum ascorbate levels in multiple cohorts**



VITAMIN C AND SLC23A1

- **Na+ dependent Vitamin C transporter**
- **rs33972313 is known to lie in exon 8 of SLC23A1 and to yield a missense change delivering a methionine (Meth/ATG) form in the presence of the rare A allele**
- **Results in by-product of a conformational change or protein failure which impairs active transport.**

Table 5

Circulating L ascorbic acid by allelic variation at *SCL23A1* in the European Prospective Investigation of Cancer study.

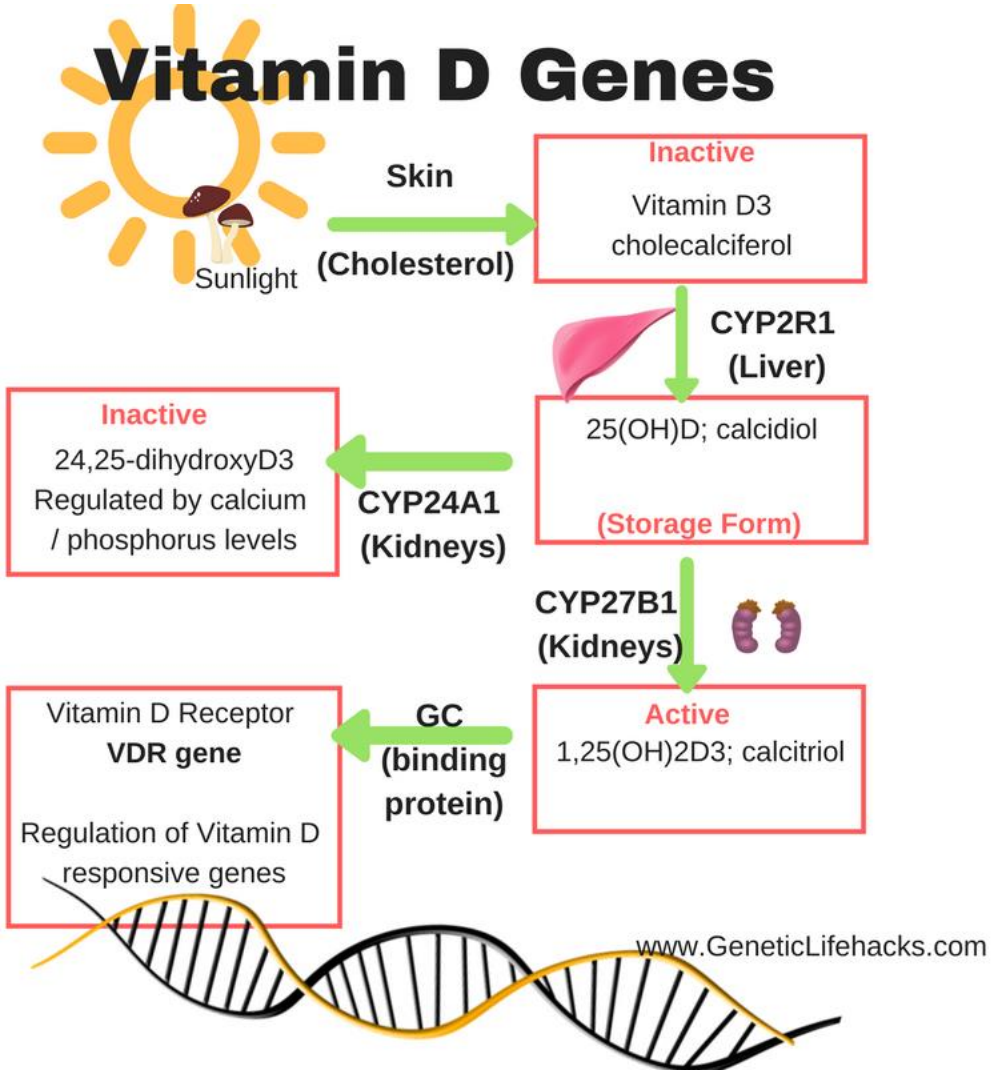
	Mean (95%CI) L-ascorbic acid				
	Genotype at rs33972313 (n=4501)				
	GG	GA	AA	Mean difference in L-ascorbic acid per minor allele	p
L ascorbic acid µmol/L	56.66 (56.08, 57.24)	48.21 (45.99, 50.43)	43.38 (28.02, 58.73)	−8.31 (−10.51, −6.11)	1.7×10^{-13}

WHAT TO DO IF SOMEONE IS CARRYING AT RISK ALLELE OF SLC23A1?

- Upto 75% reduction in SLC23A1 activity
- Upto 75% reduction in ability of cells to absorb Vitamin C
- Could mean an increased cancer predisposition
- Dietary intervention to boost Vitamin C intake

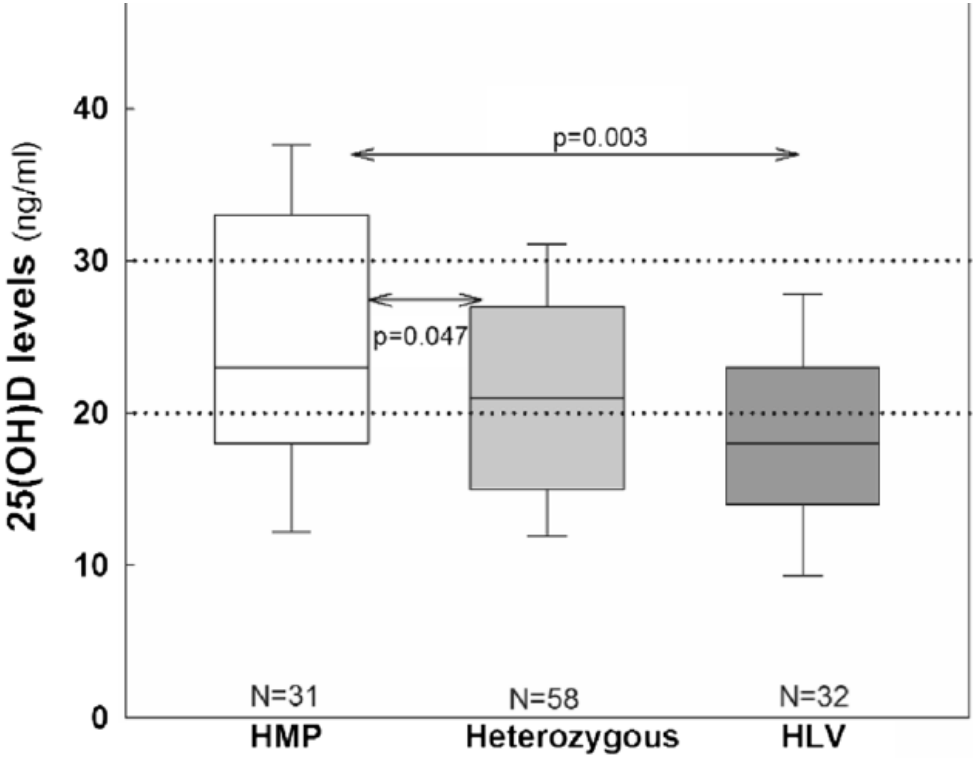
VITAMIN D AND GENETICS

- **Absorb calcium - Vitamin D, along with calcium, helps build bones and keep bones strong and healthy.**
- **Block the release of parathyroid hormone. This hormone reabsorbs bone tissue, which makes bones thin and brittle.**
- **Mutations in CYP2R1 and GC genes are associated with Vitamin D deficiency**



VITAMIN D AND CYP2R1

- **CYP2R1 is a major vitamin D 25-hydroxylase that plays a fundamental role in activation of this essential vitamin**
- **Variants that reduce CYP2R1 activity are associated with reduced Vitamin D levels**
- **G allele associated with reduced CYP2R1 activity, reduced Vitamin D levels and increased risk of diabetes**



VITAMIN D AND GC

- GC encodes for Vitamin D binding protein
- It transports vitamin D metabolites between skin, liver and kidney, and then on to the various target tissues
- Variants associated with increased risk of vitamin D deficiency
- Same variants have also been associated with an increased risk of colorectal cancer, polycystic ovarian syndrome, coronary heart disease

WHAT TO DO IF SOMEONE IS CARRYING AT RISK ALLELES OF CYP2R1 AND GC?

- Increased risk of Vitamin D deficiency
- Vitamin D supplementation
- Vitamin D supplementation has shown in a few studies to be efficacious in reducing the associated adverse health effects

VITAMIN E AND GENETICS

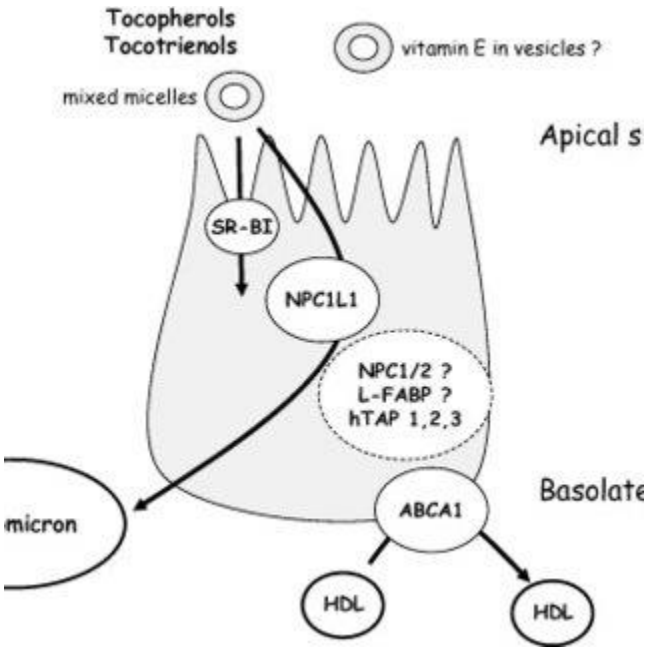
- **Vitamin E is a family of essential micronutrients composed of lipid-soluble tocopherols and tocotrienols that have potent antioxidant activity**

- **Protects against oxidative stress in vivo, and, thus, it may play a role in aging, atherosclerosis, neurodegeneration and cancer**

- **Mutations in SCARB1 AND CYP4F2 associated with Vitamin E deficiency**

VITAMIN E AND SCARB1

- **Scavenger receptor class B type I (SR-BI)**
- **Involved in transport of vitamin E across enterocytes (epithelial cells in intestine – intestinal absorption**
- **Dietary vitamin E is absorbed in intestines**
- **Mutations that compromise SCARB1 activity are correlate with vitamin E deficiency**



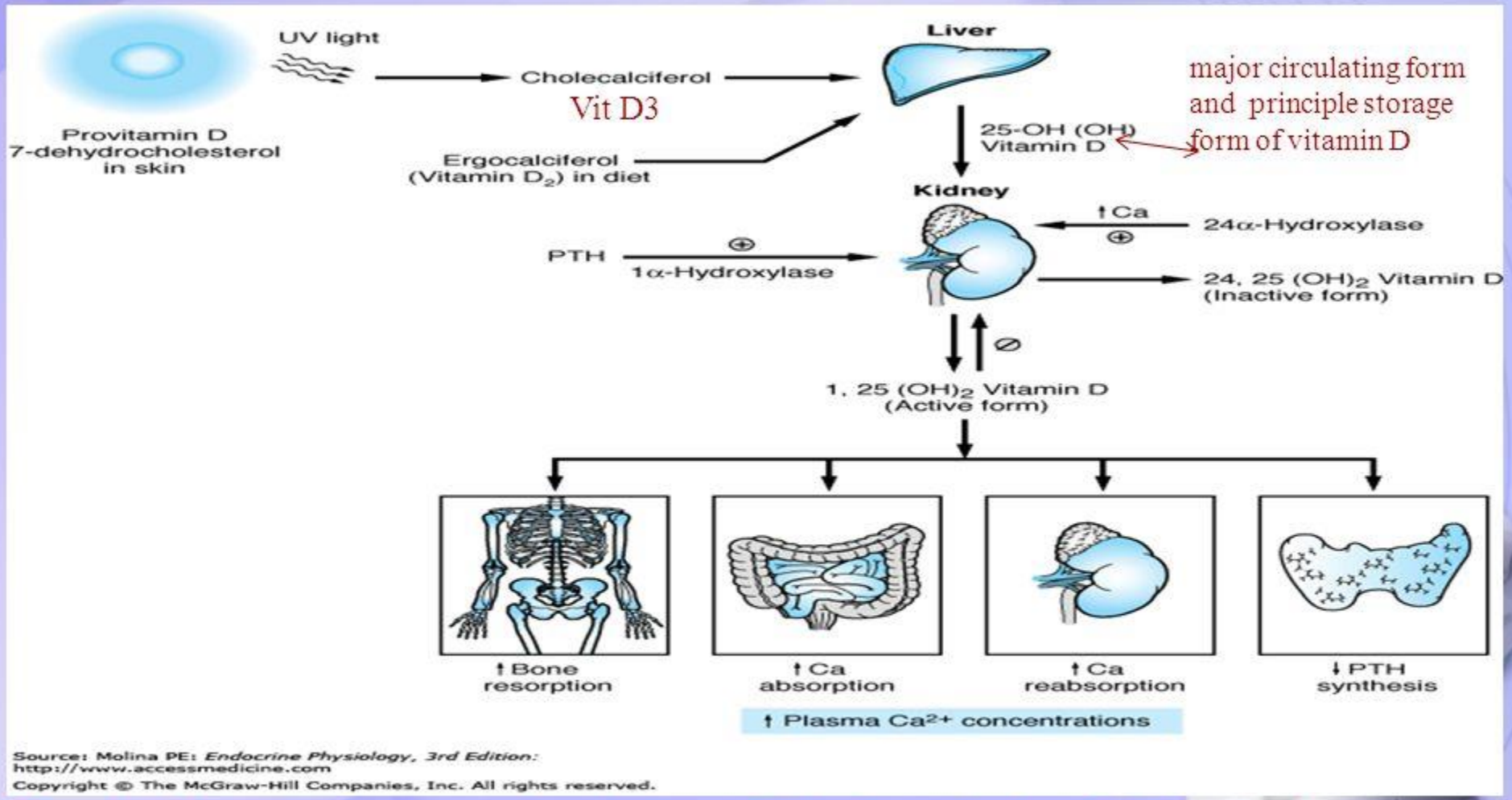
VITAMIN E AND CYP4F2

- **CYP4F2 – part of Cytochrome p450 complex**
- **Plays a role in breakdown of Vitamin E**
- **Mutations that increase CYP4F2 activity associated with reduced Vitamin E levels**
- **Mutations that decrease CYP4F2 activity associated with reduced risk of Vitamin E deficiency**
- **CYP4F2 is Vitamin K oxidase and reduced activity correlates with increased risk of Vitamin K deficiency**
- **Mutations in CYP4F2 also associated with Coronary Heart Disease**

WHAT TO DO IF SOMEONE IS CARRYING AT RISK ALLELES OF CYP4F2 AND SCARB1?

- Increased risk of Vitamin E deficiency
- Reduced anti-oxidant potential
- Increased risk of cancers, oxidative damage
- Reduced CYP4F2 -> Vitamin K deficiency
- Vitamin E supplementation

Calcium and Vitamin D



Vitamin D increases bone resorption, increases Ca^{2+} absorption from the intestine, increases renal Ca^{2+} reabsorption, and decreases the production of PTH by the parathyroid glands. The overall effect of vitamin D is to increase plasma Ca^{2+} concentrations.

GC GENE AND RISK OF CALCIUM DEFICIENCY

- GC involved in skeletal metabolism

- Encodes Vitamin D binding protein (DBP) which stores and prolongs Vitamin D half life

- Vitamin D is an important cofactor of calcium absorption in intestine and reabsorption in kidney, which plays an essential role in regulating serum calcium and phosphate homeostasis as well as bone metabolism

- DBP can also be converted to a DBP-macrophage activating factor (DBP-MAF)
- DBP-MAF plays a role in osteoclast differentiation and mediates bone resorption by directly activating osteoclasts

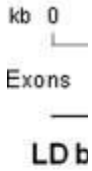
GC HAPLOTYPES

Table 1: Common phenotypic variants of DBP and associated characteristics.

Phenotype	rs7041 (D432E)	rs4588 (T436K)	DBP levels in homozygotes	25(OH) D affinity
GC1F	t (D: asp)	c (T: thr)	Lowest	Highest
GC1S	g (E: glu)	c (T: thr)	Highest	Intermediate
GC2	t (D: asp)	a (K: lys)	Intermediate	Lowest

The three most widely studied variants of DBP include GC1F, GC1S, and GC2, which are distinguished by their SNPs rs7041 and rs4588. The associated nucleotide and amino acid changes are presented, along with known data on DBP levels in homozygotes and affinity for 25(OH) D (derived from Powe et al. [9] and Arnaud and Constans [7]). Conflicting data regarding these relationships remain [10].

a



b

	rs7041 (E416D)	rs4588 (T420K)	Freq. (%)
Haplotype1 Gc1s	**G** (Glu)	**C** (Thr)	**56**
Haplotype2 Gc2	**T** (Asp)	**A** (Lys)	**27**
haplotype3 Gc1f	**T** (Asp)	**C** (Thr)	**16**

GC HAPLOTYPES

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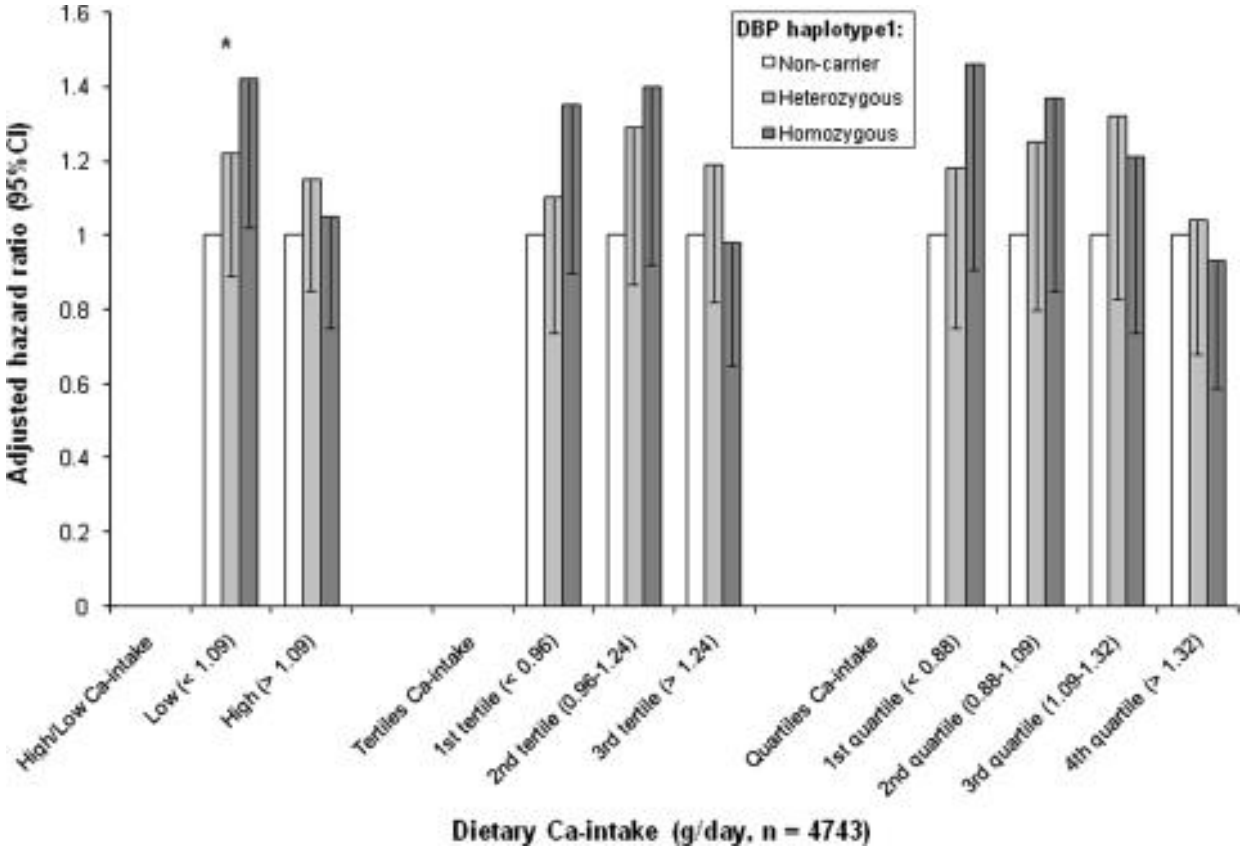
GC GENE AND RISK OF OSTEOPOROSIS

- GC haplotype 1 associated with increased risk of osteoporosis with low Calcium Intake



WHAT TO DO IF SOMEONE IS CARRYING AT RISK ALLELES OF GC?

- Elevated risk of Calcium deficiency
- Elevated risk of osteoporosis
- Calcium supplementation
- Are they predisposed to Vitamin D deficiency?
- Vitamin D and Calcium supplementation

Iron

- Element (Fe)
- Molecular weight 56
- Abundance
- May be 2+ or 3+
  - Ferrous (2+) “reduced” - gained an electron
  - Ferric (3+) “oxidised” - lost an electron

$$Fe^{+++} + e^{-} \leftrightarrow Fe^{++}$$

- Redox states allows activity passing electrons around body
- Redox change required for iron metabolism

Iron functions

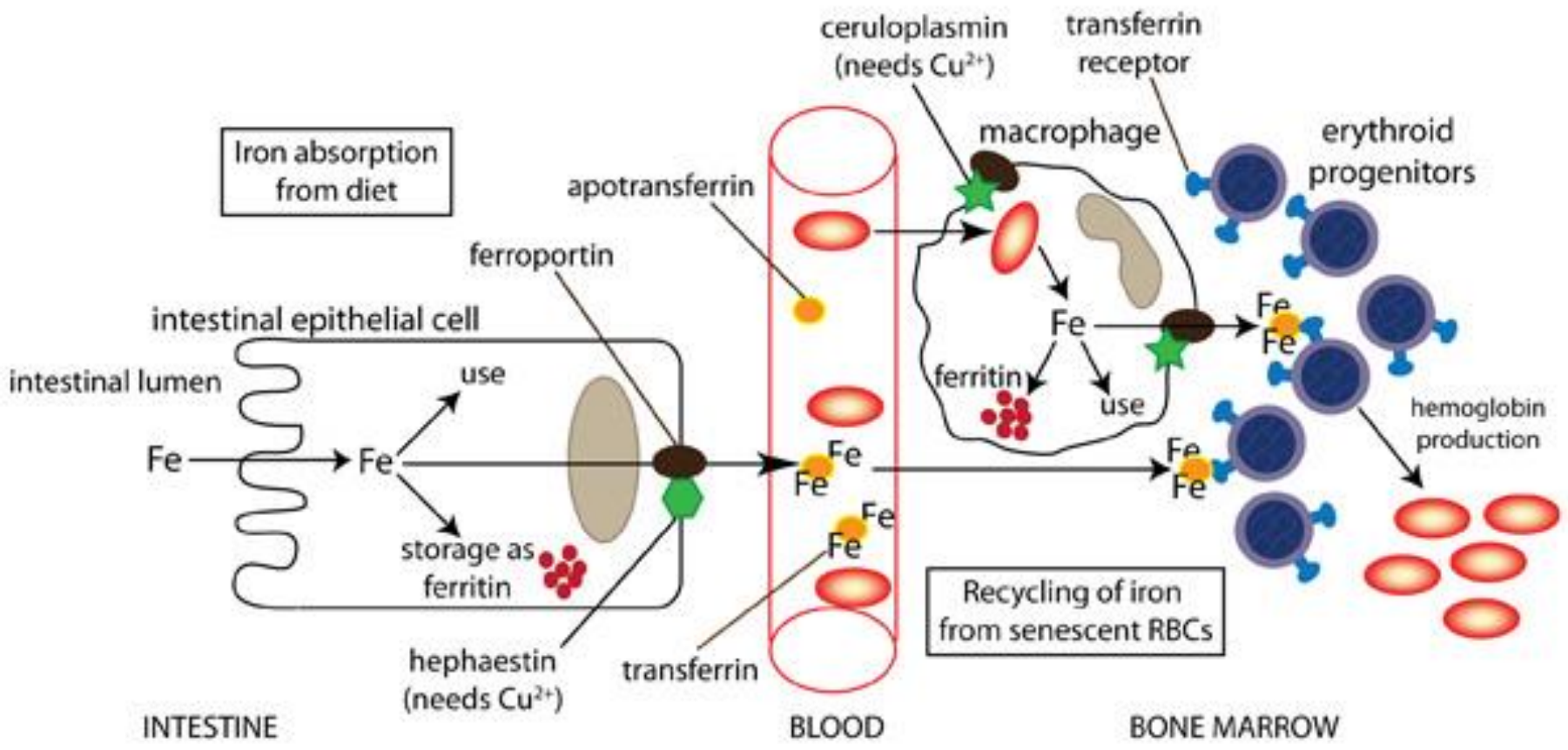
- Oxygen carriers
  - haemoglobin
- Oxygen storage
  - Myoglobin
- Energy Production
  - Cytochromes (oxidative phosphorylation)
  - Krebs cycle enzymes
- Other
  - Liver detoxification (cytochrome p450)

- **An essential element**

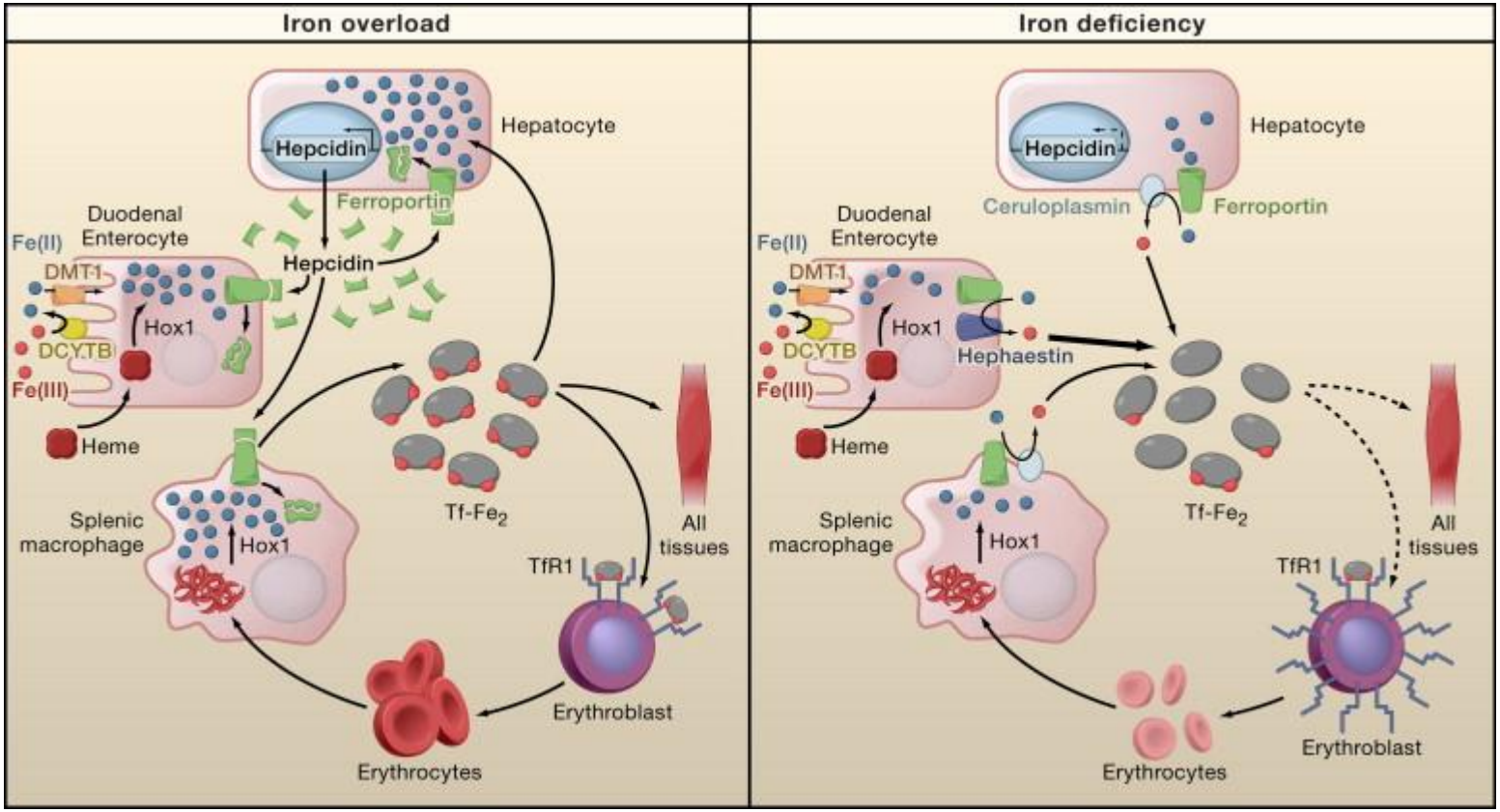
Iron Toxicity

- Iron can damage tissues
- Catalyzes the conversion of hydrogen peroxide to free-radical ions
- Free-radicals can attack:
  - cellular membranes
  - Proteins
  - DNA
- Iron excess possibly related to cancers, cardiac toxicity and other factors

IRON METABOLISM



IRON REGULATION



What Is Hemochromatosis ?

- Disorder of iron overload
  - Hereditary hemochromatosis (HH)
  - Acquired hemochromatosis – due to other diseases, increased iron ingestion, iron infusions, treatment dependent on cause

- HH: genetic defect in iron metabolism
  - Excess iron absorbed from the gut
  - Symptoms due to pathologic deposition of iron in body tissue = iron overload

Symptoms – Traditional Concept

- Classic Triad – LESS THAN 15% PATIENTS:
  - Cirrhosis (hepatic damage)
  - Diabetes (type II) (pancreatic damage)
  - Bronzing of skin (hyperpigmentation)

- Traditional triad means diagnosed too late!
- Damage may be only partially reversible
- Goal is to detect the disease BEFORE organ damage occurs

Non-Specific Symptoms and Signs

- **Liver**: hepatomegaly, elevated liver enzymes
- **Cardiac**: myocardial infarction, cardiomyopathy
- **Endocrine**: impotence/amenorrhea, diabetes
- **Musculoskeletal**: arthritis/arthralgia
- **Fatigue**: unexplained, severe and chronic

Generally not evident until 40-60 years of age

Some patients may present earlier

The Genetics of Hemochromatosis

- *HFE*– associated Hemochromatosis accounts for > 90% of cases and is the most common adult onset form:
- Autosomal recessive inheritance
- C282Y mutation
  - Carrier rate 1 in 7 - 10 Caucasians
  - Incidence 1 in 200 - 400
- Penetrance is low ie not everyone with the genotype will develop the disease

Autosomal Recessive Inheritance

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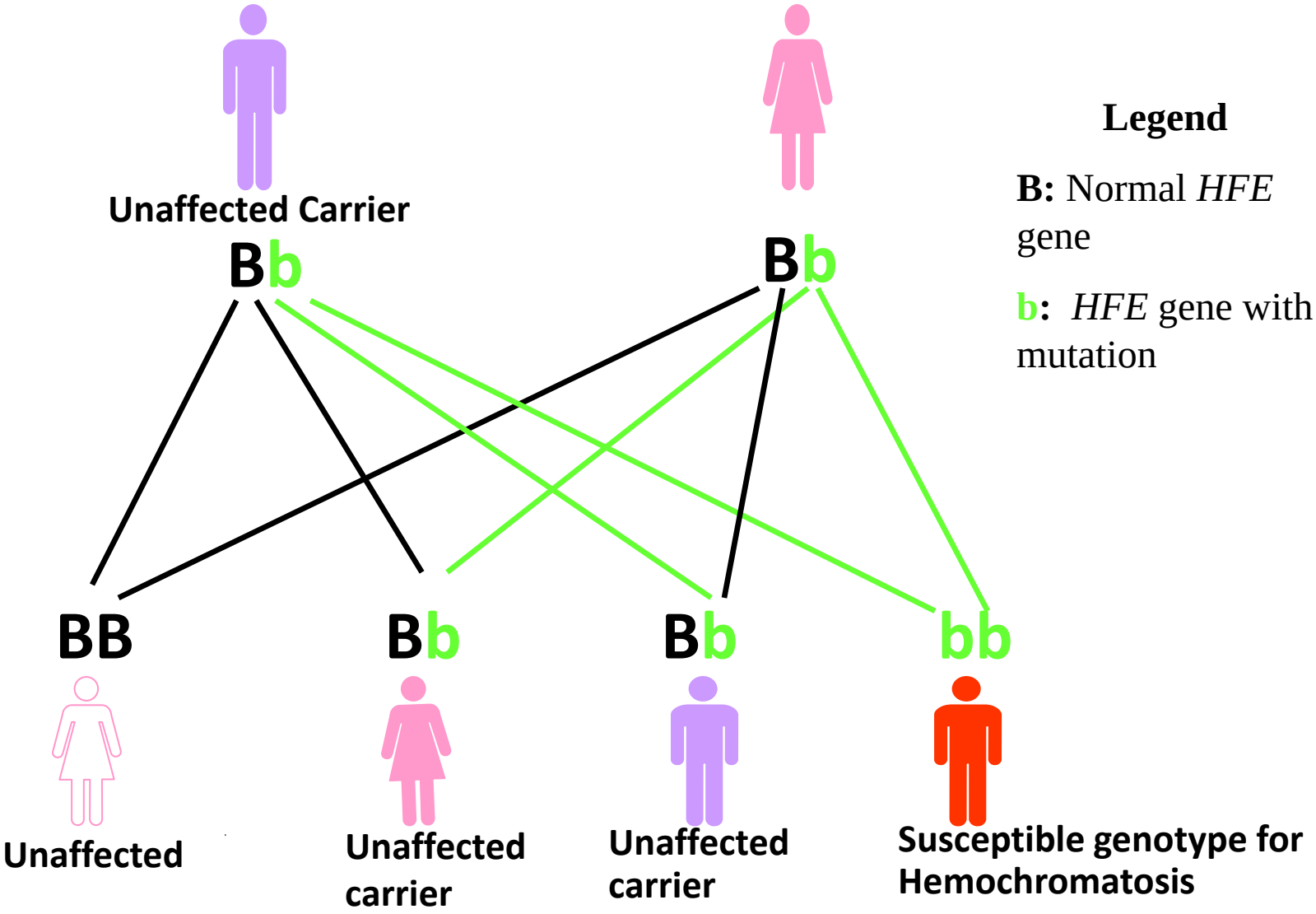


Legend

B: Normal *HFE* gene

b: *HFE* gene with mutation

The *HFE* Gene

- *HFE* gene on chromosome 6
  - Involved in iron homeostasis It is thought that this protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin.
  - *HFE* protein normally limits amount of iron uptake by gut and regulates amount of iron stored in the tissues
- Two common mutations in *HFE*
  - C283Y allele
  - H63D allele
  - 2% of heterozygotes for both develop disease
- *HFE* gene mutations produce altered HFE protein unable to properly regulate iron metabolism - results in an excess of iron storage in tissues

SLC17A1 AND IRON OVERLOAD

- Sodium-dependent phosphate transport protein 1 is a protein that in humans is encoded by the SLC17A1 gene
- Its major function is in kidney
- The role in iron regulation is not understood
- Certain variants in SLC17A1 have been associated with iron overload

WHAT TO DO IF SOMEONE IS AT RISK OF IRON OVERLOAD?

- Risk of iron overload does not mean diagnosis – low penetrance
- Iron levels may need to be monitored regularly
- Also associated with increased arthritis risk
- First signs of iron overload - joint pain, fatigue, general weakness, weight loss, and stomach pain

IRON DEFICIENCY AND GENETICS

- **Iron deficiency anemia occurs when your body doesn't have enough iron.**
- **Iron is important because it helps you get enough oxygen throughout your body.**
- **Your body uses iron to make hemoglobin. Hemoglobin is a part of your red blood cells. Hemoglobin carries oxygen through your body.**
- **If you do not have enough iron, your body makes fewer and smaller red blood cells. Then your body has less hemoglobin, and you cannot get enough oxygen.**

IRON DEFICIENCY AND GENETICS

- **Mutations in TMPRSS6, TF and TFR2 genes are associated with increased risk of iron deficiency and anemia**

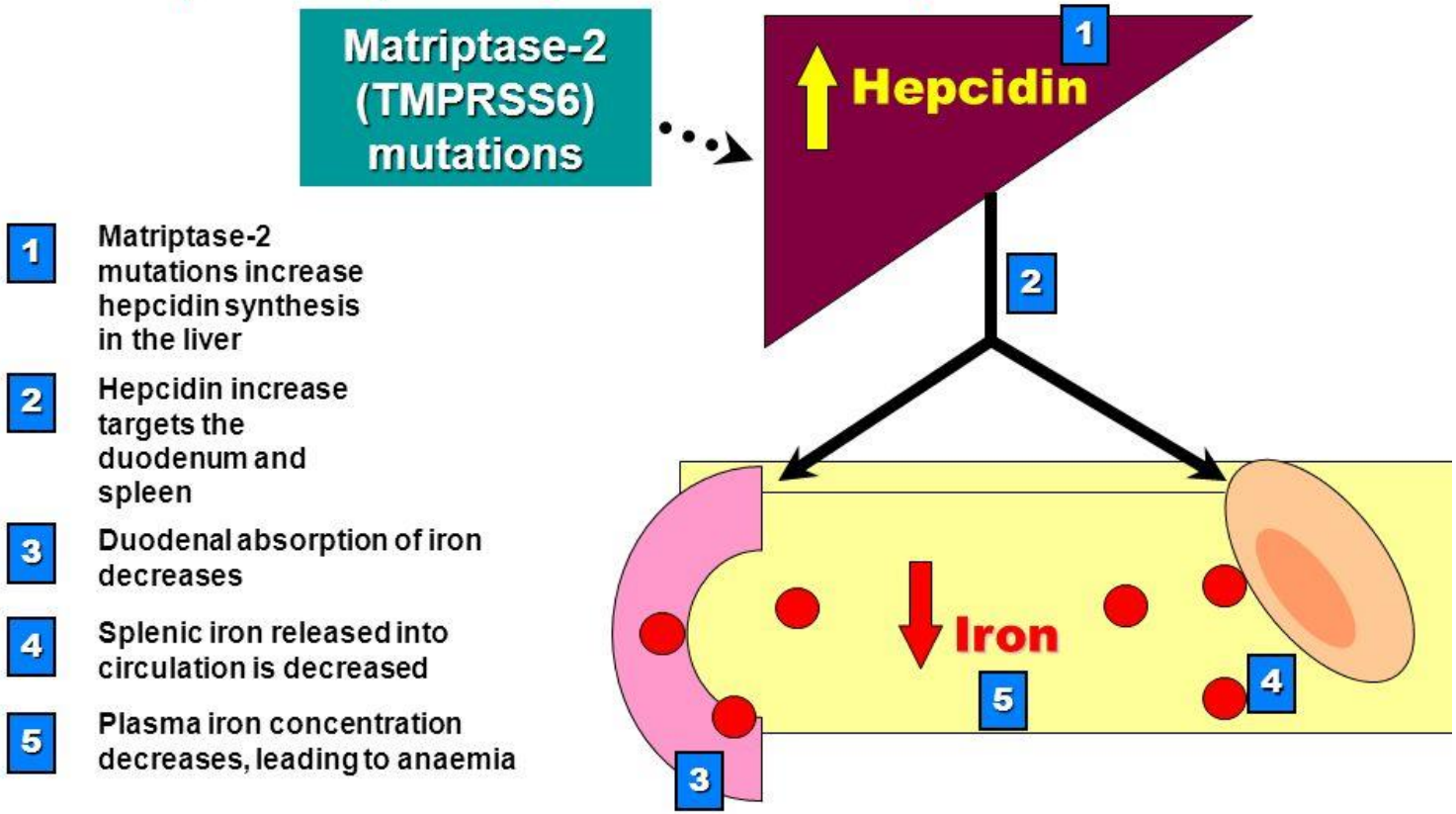
- **The TMPRSS6 gene encodes matriptase-2, a serine protease that represses hepcidin. Hepcidin inhibits iron transport by binding to the iron export channel on cells.**

- **TF encodes for Transferrin which has the function of transporting iron**

- **The main function of TFR2 is to help iron enter liver cells (hepatocytes). On the surface of hepatocytes, the receptor binds to a protein called transferrin, which transports iron through the blood to tissues throughout the body. When transferrin binds to transferrin receptor 2, iron is allowed to enter the cell.**

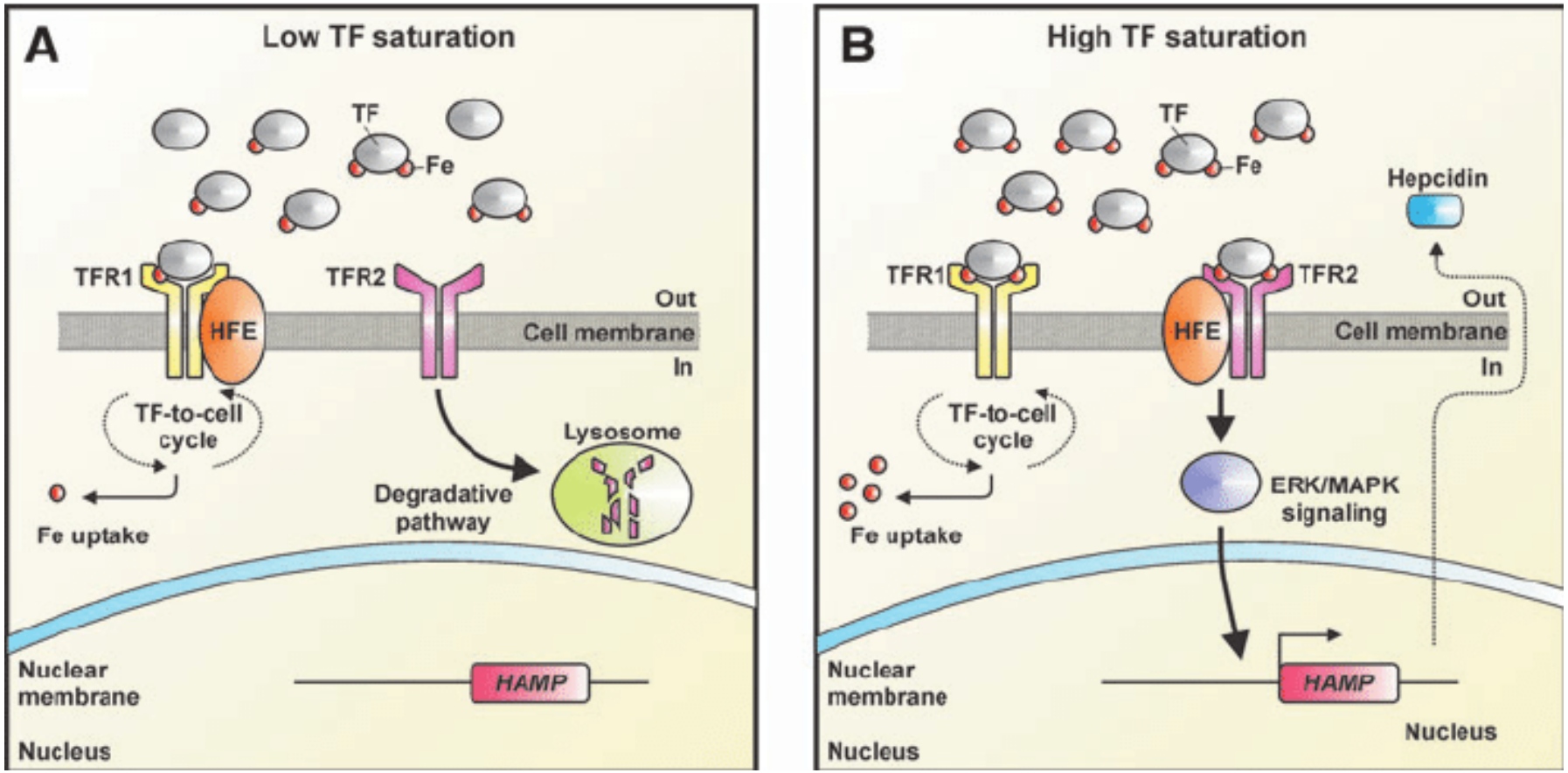
IRON DEFICIENCY AND GENETICS

Iron-Refractory Iron-Deficiency Anaemia (IRIDA)—Hepcidin Overproduction



Finberg KE, et al. *Nat Genet.* 2008;40:569-571.

TF AND TFR2 GENETICS AND ANEMIA



WHAT TO DO IF SOMEONE IS AT RISK OF IRON DEFICIENCY?

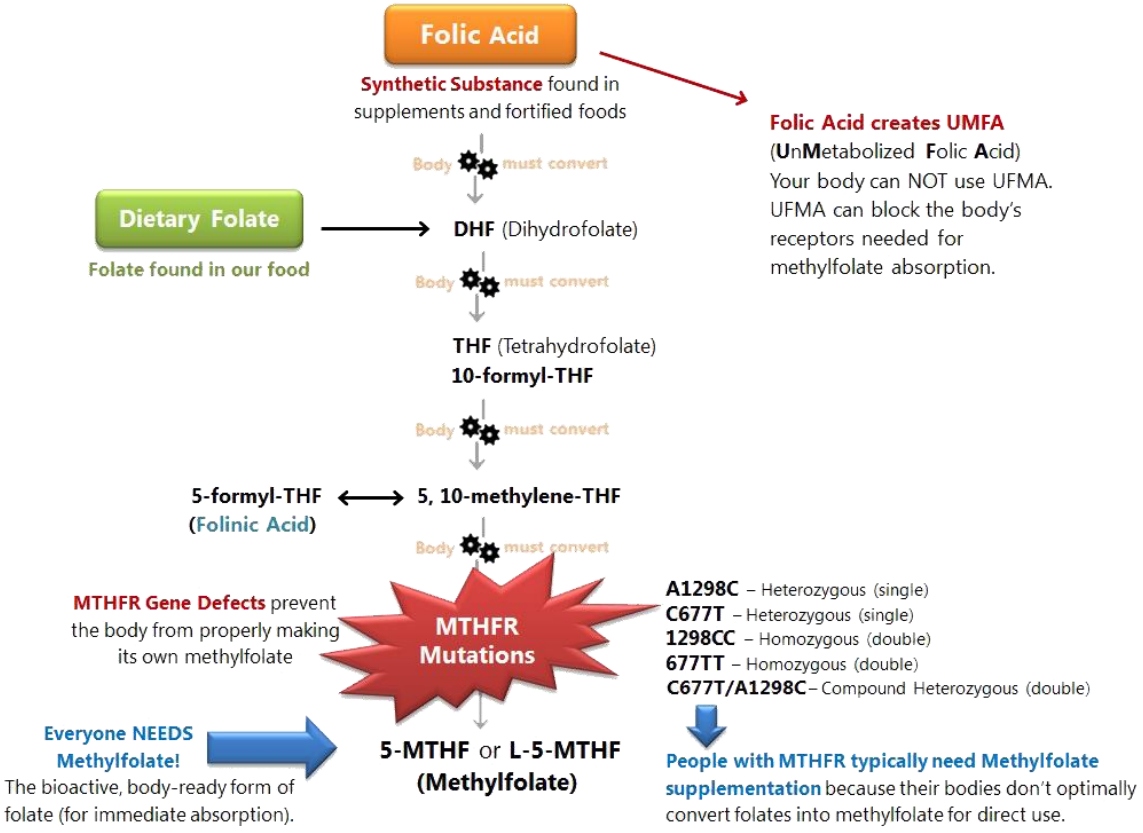
- **Iron supplementation oral – atleast 2 cycles**
- **Monitoring of iron levels**
- **Watch for earliest signs of anemia**
- **Ascorbic acid oral supplementation has also shown efficacy**

GENETICS OF MAGNESIUM, ZINC, SELENIUM

MAGNESIUM	MUC1 encodes a protein which is part of mucus layer changes in which can impact nutrient absorption including magnesium	**TC** **AG**
	SHROOM3 regulates cell shape in certain tissues and associated with Magnesium deficiency	**TT** **TC** **AA**
	TRPM6 plays a role in epithelial magnesium transport and in the active magnesium absorption in the gut and kidney.	
	DCDC5 associates with magnesium deficiency	
	ATP2B1 encodes enzyme for ion transport	
SELENIUM	DMGDH, AGA and SLC39A11 polymorphisms show a strong association with serum selenium levels	**TC** **CC** **GG**
ZINC	CA1 is a zinc metalloenzyme	**GG**
	PPCDC shows association with zinc deficiency	**TC**
	LINC01420 shows association with zinc deficiency	**TT**

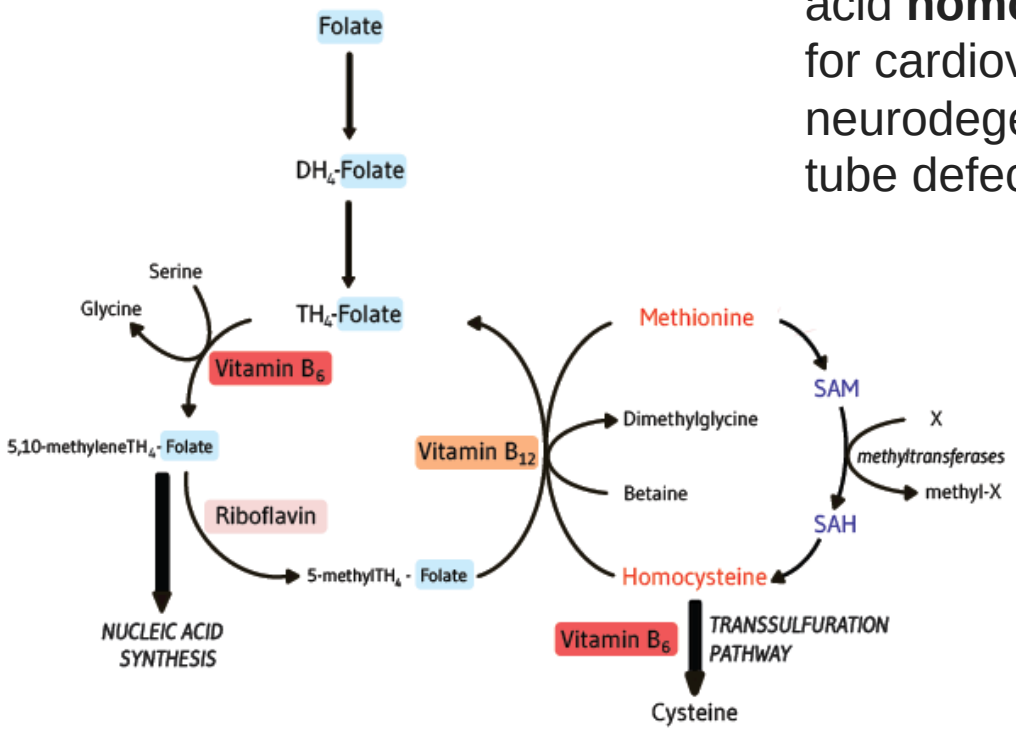
FOLATE AND GENETICS

Essential nutrient, deficiency of which can lead to anemia and in pregnant females can lead to neural brain defects in babies



FOLATE AND HOMOCYSTEINE

Figure 2. Overview of One-carbon Metabolism



5,10-methylenetetrahydrofolate is required for the synthesis of nucleic acids, and 5-methyltetrahydrofolate is required for the formation of methionine from homocysteine. Methionine, in the form of methyl donor S-adenosylmethionine (SAM), is essential to many biological methylation reactions, including DNA methylation. Methylenetetrahydrofolate reductase (MTHFR) is a riboflavin (FAD)-dependent enzyme that catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. *SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; TH_4-Folate, Tetrahydrofolate.*

Elevated level of the nonprotein amino acid **homocysteine** (Hcy) is a risk factor for cardiovascular diseases, neurodegenerative diseases, and neural tube defects

Cancer

- Since folic acid is involved in the synthesis, repair and functioning of DNA (our genetic map), a deficiency may result in damage to DNA that leads to cancer.
- A relationship between folic acid and several types of cancers has been observed in several population-based studies but is most clearly defined for colorectal cancer and colorectal adenomas.

Colon Cancer

- Nurses' Health Study cohort
  - After 14 years of follow-up, women consuming at least 400 mcg/d of total folate had a 31% decreased risk of colon cancer.
  - After 15 years of taking a vitamin supplement with folic acid, relative risk of colon cancer was decreased by 75%.

Colon Cancer

- Nurse's Health Study and Health Professionals Follow-up Study.
    - A 30-40% decreased risk for colorectal adenomas was found with total folate intakes greater than 700 mcg/d.

Cancer

- Epidemiologic studies provide support for the hypothesis that decreased methyl group availability may contribute to cancer risk.
- Risks were exacerbated by methyl deplete diets: high alcohol, low folate, low methionine.

Alzheimer's Disease and Autism

- Recent research suggests that folate deficiency and a high homocysteine level may increase the risk for development of Alzheimer's disease and vascular dementia.
- More clinical trials are needed.

- Studies also implicate MTHFR mutations with risk of autism

Folic Acid Deficiency

- Folic acid deficiency can lead to impairment of cell division, accumulation of possibly toxic metabolites such as homocysteine, and impairment of methylation reactions involved in the regulation of gene expression.

MTHFR VARIATION – FOLATE SUPPLEMENTATION

Close to half the population can be carrying MTHFR variants which reduce enzymatic activity

MTHFR variant genes are common!
Percent of a mixed population containing 677 and 1298 variant genes.[4]

	Normal 677	677 variant heterozygous	677 variant homozygous
Frequency % found in a mixed population	44%	41%	15%
	Normal 1298	1298 variant heterozygous	1298 variant homozygous
Frequency % found in a mixed population	46%	41%	13%

Genotype	677CC 2 normal 677s	6T7CT heterozygous one 677 variant	677TT homozygous two 677 variants
1298AA two normal 1298s	100% enzyme acitivity	66% enzyme acitivity	25% enzyme acitivity
1298AC heterozygous one 1298 variant	83% enzyme acitivity	48% enzyme acitivity	not analyzed
1298CC homozygous two 1298 variants	61% enzyme acitivity	not analyzed	not analyzed

Adapted from data presented by van der Put et.al.[3]

WHAT DOES THIS MEAN?

If you have the MTHFR variant which reduces enzymatic activity, dietary supplementation with folate may not be enough, instead supplementation with Methylfolate is likely to be needed.

NUTRITION GENETICS

- **Genetics can identify which nutrients one has an heightened predisposition to develop deficiency for**
- **Nutritional plans need to incorporate nutrition genetics to prevent nutritional deficiencies**
- **Genetics can identify which source of nutrients will be absorbed by the individual and which wont**
- **Cannot have one plan fits all due to differences in genetics of nutrient transportation and absorption**

REVIEW

VITAMIN	GENE	ENZYME ACTIVITY
VITAMIN A	BMCO1 - enzyme that converts beta carotene into active Vitamin A	Reduced
VITAMIN B6	NBPF3 is associated with the synthesis of NBPF3, a hormone found to be associated with the clearance of vitamin B6 from the body	Elevated
VITAMIN B12	FUT2 plays a role in the cellular transport of B12	Reduced
CHOLINE	PEMT is needed for synthesis of phosphatidylcholine	Reduced
VITAMIN C	SLC23A1 encodes for a transporter protein needed for vitamin C absorption	Normal
VITAMIN D	CYP2R1 plays a role in activation of Vitamin D GC plays a role in cellular transportation of Vitamin D	Reduced (CYP2R1) Reduced (GC)
VITAMIN E	SCARB1 is involved in transport of vitamin E across enterocytes CYP4F2 is involved in catabolism of vitamin E	Reduced (SCARB1) Elevated (CYP4F2)
FOLATE	MTHFR converts folate into an active form utilized by body	Reduced

REVIEW

CALCIUM	GC plays a role in Vitamin D transportation and adequate Vitamin D needed for Calcium absorption	**Reduced**
IRON OVERLOAD	SLC17A1- certain variants correlate with iron overload HFE regulates Hepcidin, which regulates iron absorption and release	**Reduced**
LOW IRON	TMPRSS6 helps regulate iron balance TFR2 helps iron enter into cells TF plays a role in iron transfer to body	**Normal**
MAGNESIUM	MUC1 encodes a protein which is part of mucus layer changes in which can impact nutrient absorption including magnesium SHROOM3 regulates cell shape in certain tissues and associated with Magnesium deficiency TRPM6 plays a role in epithelial magnesium transport and in the active magnesium absorption in the gut and kidney. DCDC5 associates with magnesium deficiency ATP2B1 encodes enzyme for ion transport	**N/A**

FOOD INTOLERANCE

IS CAFFEINE GOOD FOR YOU?

GLUTEN INTOLERANCE – ARE YOU REALLY ?

LACTOSE INTOLERANCE

American Caffeine Consumption

Each year Americans consume 45 millions pounds of caffeine.

- On average each person consumes 2.6 cups of coffee a day or 363.5 mg of caffeine.

- In the US, more than 80% of adults consume caffeine on a daily basis.
  - Among individuals that do not drink caffeine the average intake is still ~91mg/day

- Over 450,000,000 cups of coffee are consumed in the USA every day!

Fast Facts about Caffeine

- Each year 120,000 tons of caffeine are consumed.
- The average daily consumption of caffeine among adults is 200 mg/day.
- Women metabolize caffeine about 25% faster than men.
- Contrary to popular belief, caffeine (or coffee) won't help someone sober up if they have had too much to drink

Where is Caffeine found?

- Harvested from plants but can be synthetically made.
- Not only found in coffee and energy drinks, but also in some unlikely places like:
  - chocolate, gum, and migraine medicine.
- Concentration can vary depending on the source, where it comes from, and how it is made. (Table 1)

Table 1: Caffeine Content in a Variety of Sources.

	Serving Size (fl. oz)	Caffeine content per Serving (mg)
Coffee (Brewed)	5	40-180
Decaf Coffee	5	2-5
Starbucks Coffee Grande	16	330
Espresso	1	64
Tea	5	24-50
Coca Cola Classic	12	35
Diet Coke	12	47
Mountain Dew	12	54
Pepsi	12	38
Diet Pepsi	12	35
Red Bull	8.3	80
Rockstar	8	80
Full Throttle	8	72
Hershey's Chocolate Bar	1.55 oz	9
Excedrin, Extra Strength	2 tablets	130
NoDoz Maximum Strength	1 tablet	200
Jolt Caffeinated Gum	1 stick	35

Caffeine Chemistry

Molecular Formula:
C8H10N4O2

Molecular Weight : 194.19

Medically known as
trimethylxanthine.

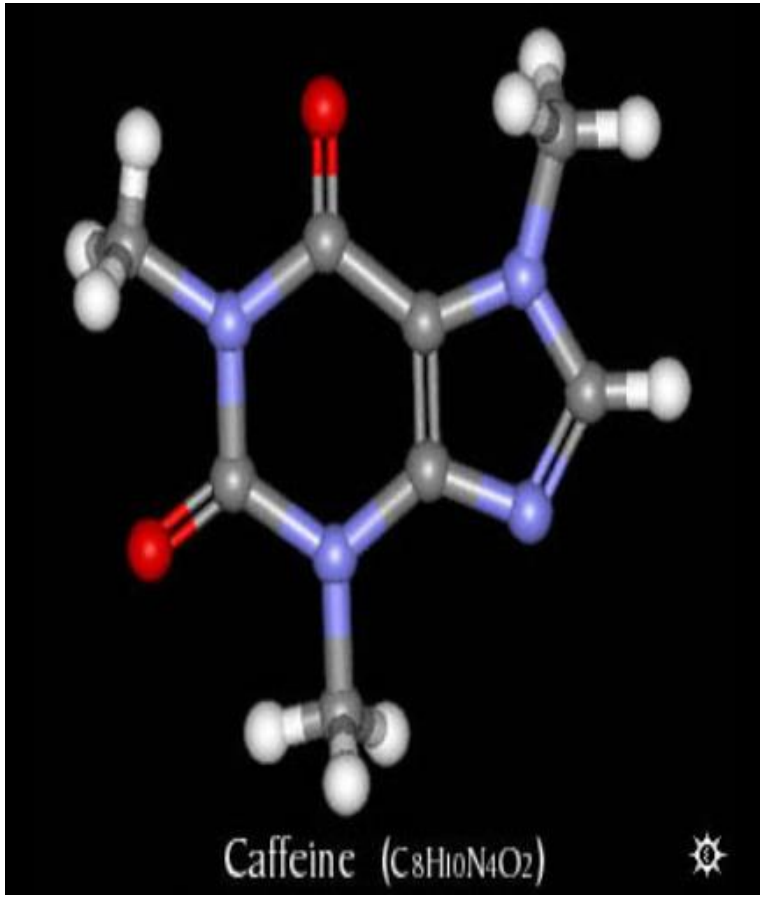


Figure 1: Caffeine Structure

Absorption

- Absorption from the GI tract takes approximately 45 minutes while peak plasma plasma concentration peaks 15 to 120 min after consumption

- Caffeine can pass through all types of membranes because it is hydrophobic in nature

- There is no blood-brain or blood-placental barrier.
  - Cause of premature birth weight in infants

Metabolism

- Takes place in the liver with help from Cytochrome P450, where it is metabolized into three seperate substances

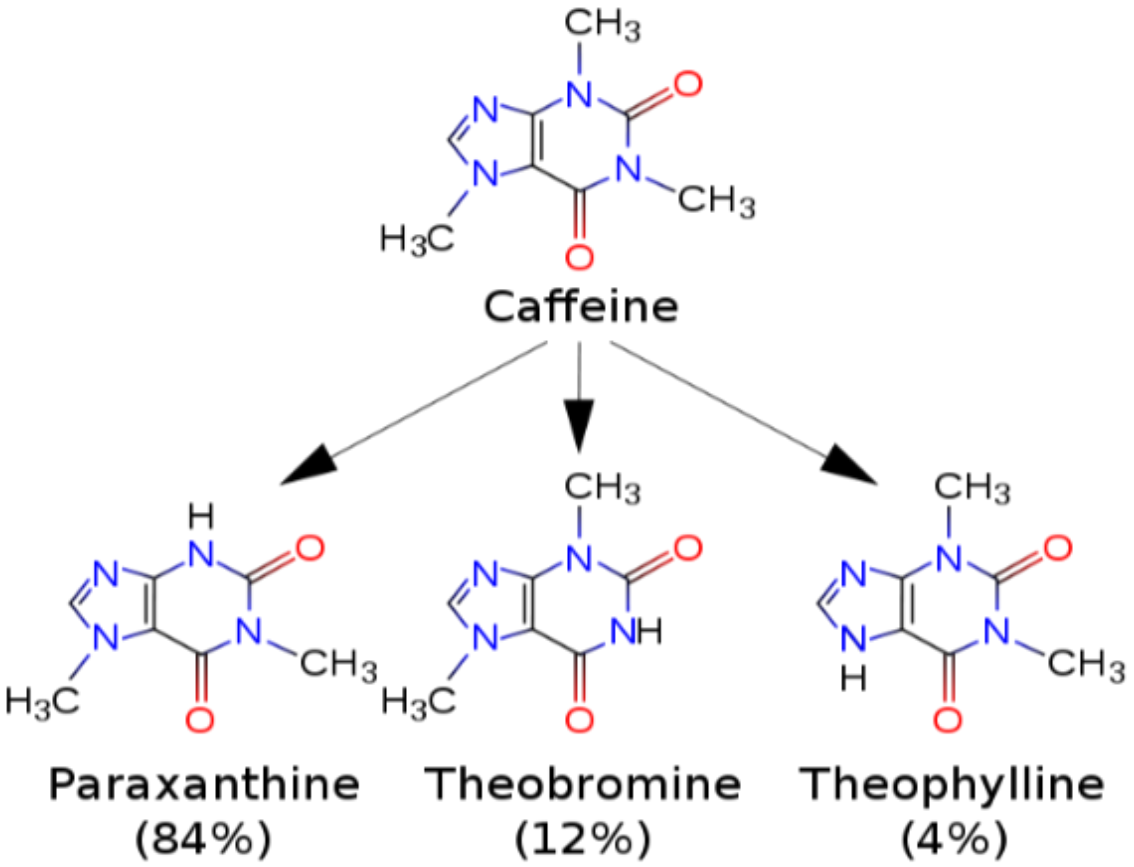


Figure 2: Caffeine derivatives

Metabolism

- Paraxanthine: Increases lipolysis, leading to elevated glycerol and free fatty acid levels in the blood plasma. Also increases the amounts of Ca++ in the skeletal muscle

- Theobromine: Dilates blood vessels and mildly increases urine production.

- Theophylline: Relaxes smooth muscles of the bronchi, and is used to treat asthma.Can cause nausea and irregular heartbeat

Each of these metabolites is further metabolized and then excreted in the urine.

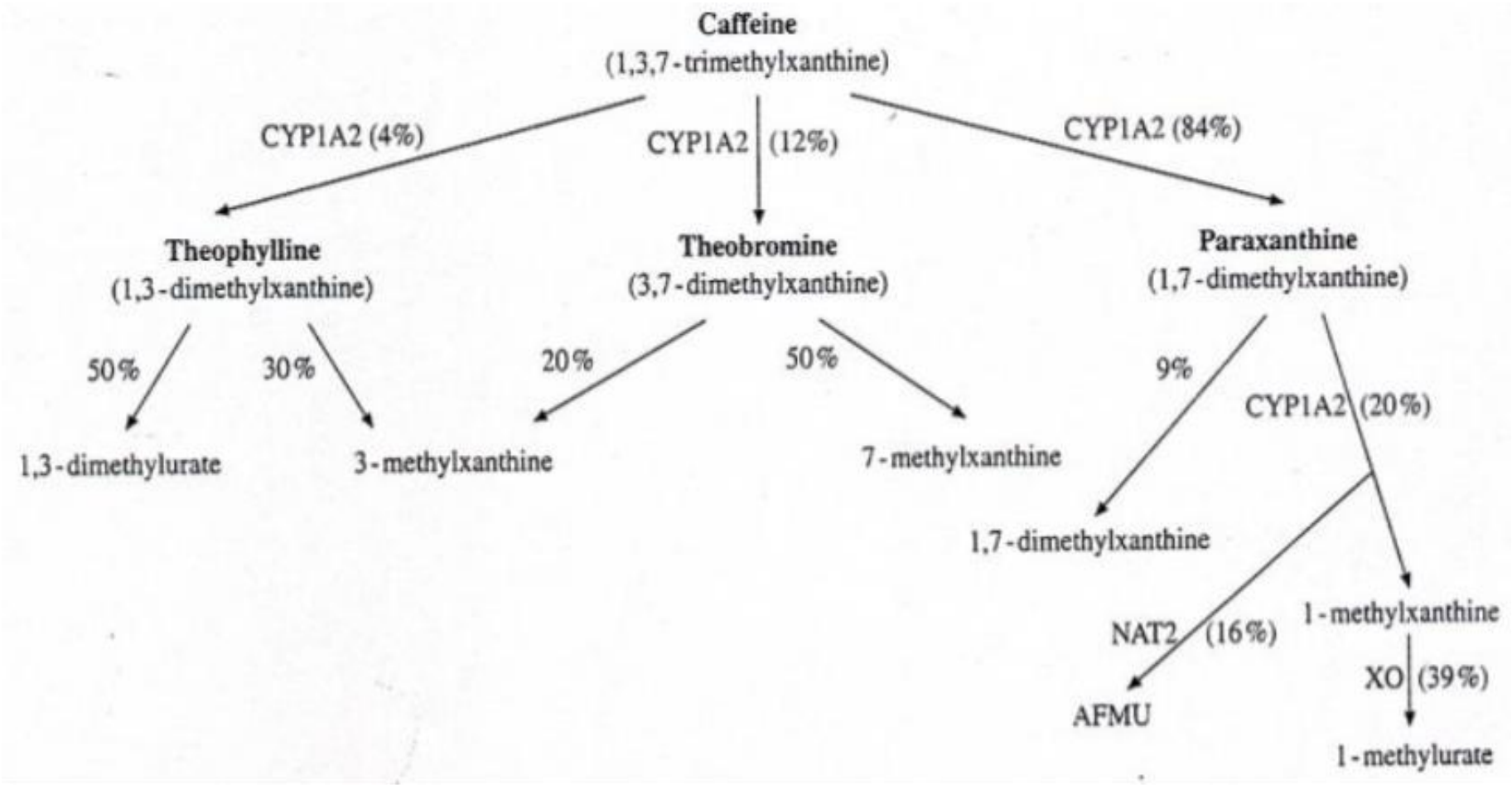


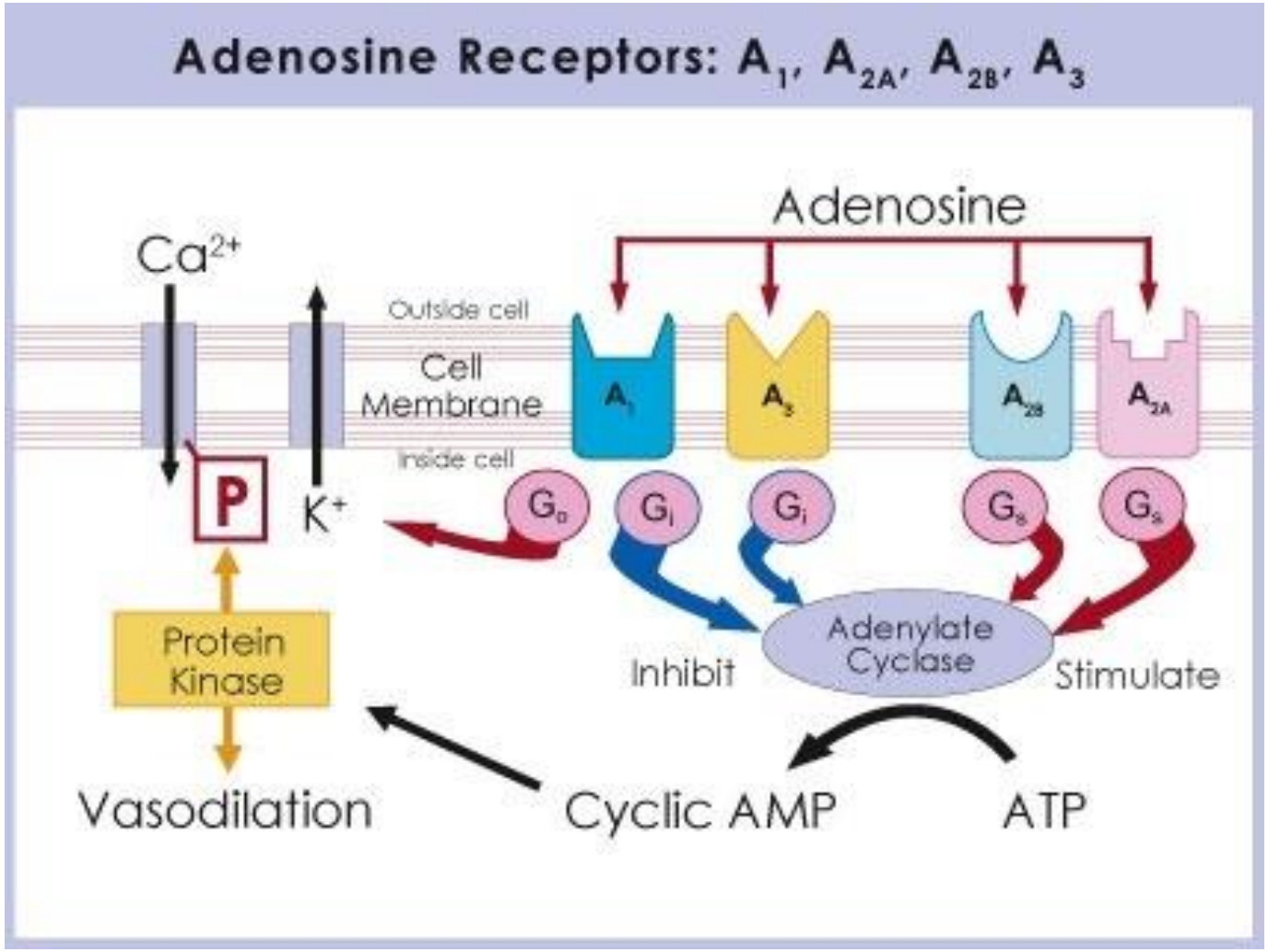
Figure 1: Metabolism of Caffeine

Caffeine and Adenosine: a battle over receptor sites.

- Adenosine is the primary sleep mechanism and causes drowsiness because it slows neural cell activity.

- Caffeine increases alertness by binding to adenosine receptors in the brain, inhibiting the normal response.

Caffeine and Adenosine



Mechanism of Action

- Primarily stimulates the CNS.
- Tolerance to caffeine is associated with increased adenosine receptor activity and a shifting of A1 receptors to a high affinity state
- Phosphodiesterase inhibition - this enzyme is responsible for the breakdown of cAMP and therefore this action of the methylxanthines leads to increased cAMP

Mechanism of Action

- 2nd messenger functions. Action at Ca++ channels to increase entry of Ca++ into cells and to decrease sarcolemma sequestration of Ca++ - affects cardiovascular function

- This may be related to the weak positive inotropic effect of the drug at high dose rates. Binding to GABA receptors at the benzodiazepine site.

Half-life

- Humans: 2.5-5.7 hours.
  - The same study showed that individuals with a compromised liver have an extended half life.
  - During neonatal development half-life increases to 100 hours due to decreased activity of cytochrome P-450.

- Rats/Mouse: 0.7- 1.2 hours

- Monkey: 3-5 hours

CAFFEINE METABOLISM AND CYP1A2

A single mutation in CYP1A2 determines whether enzymatic activity will be low or high.

Individuals with *1F allele – Reduced enzymatic activity – Slow caffeine metabolism – Caffeine in blood for longer time periods – Adverse effects

Individuals with *1A allele – Increased enzymatic activity – Rapid caffeine metabolism – Caffeine in blood for shorter time period - Beneficial

CYP1A2 AND RISK OF BLOOD PRESSURE WITH COFFEE INTAKE

ODDS RATIO FOR HYPERTENSION RISK

CYP1A2 GENOTYPE	NO COFFEE	1-3 CUPS/DAY	>4 CUPS/DAY
SLOW (1F)	1	1.72	3
FAST (1A/1A)	1	0.8	0.36

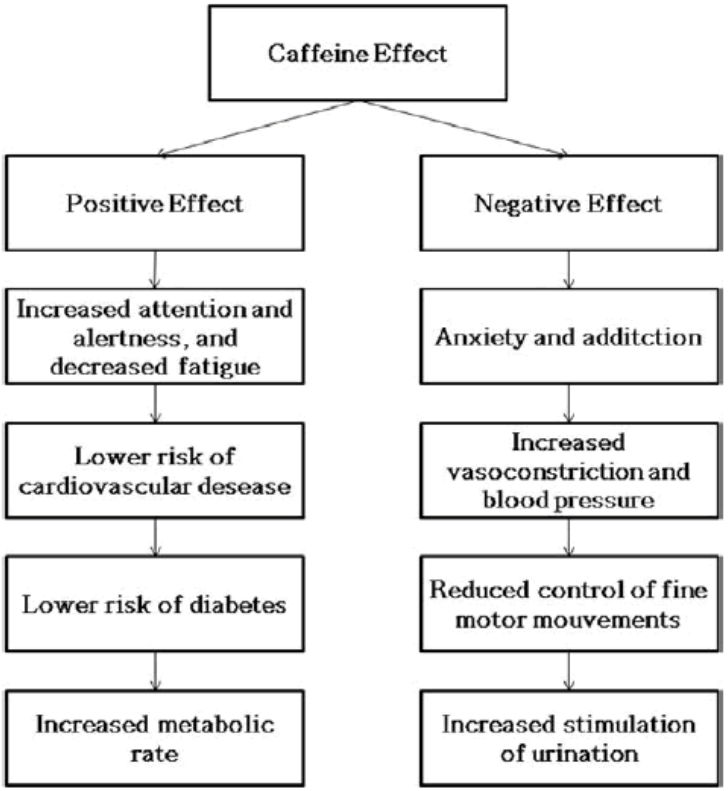
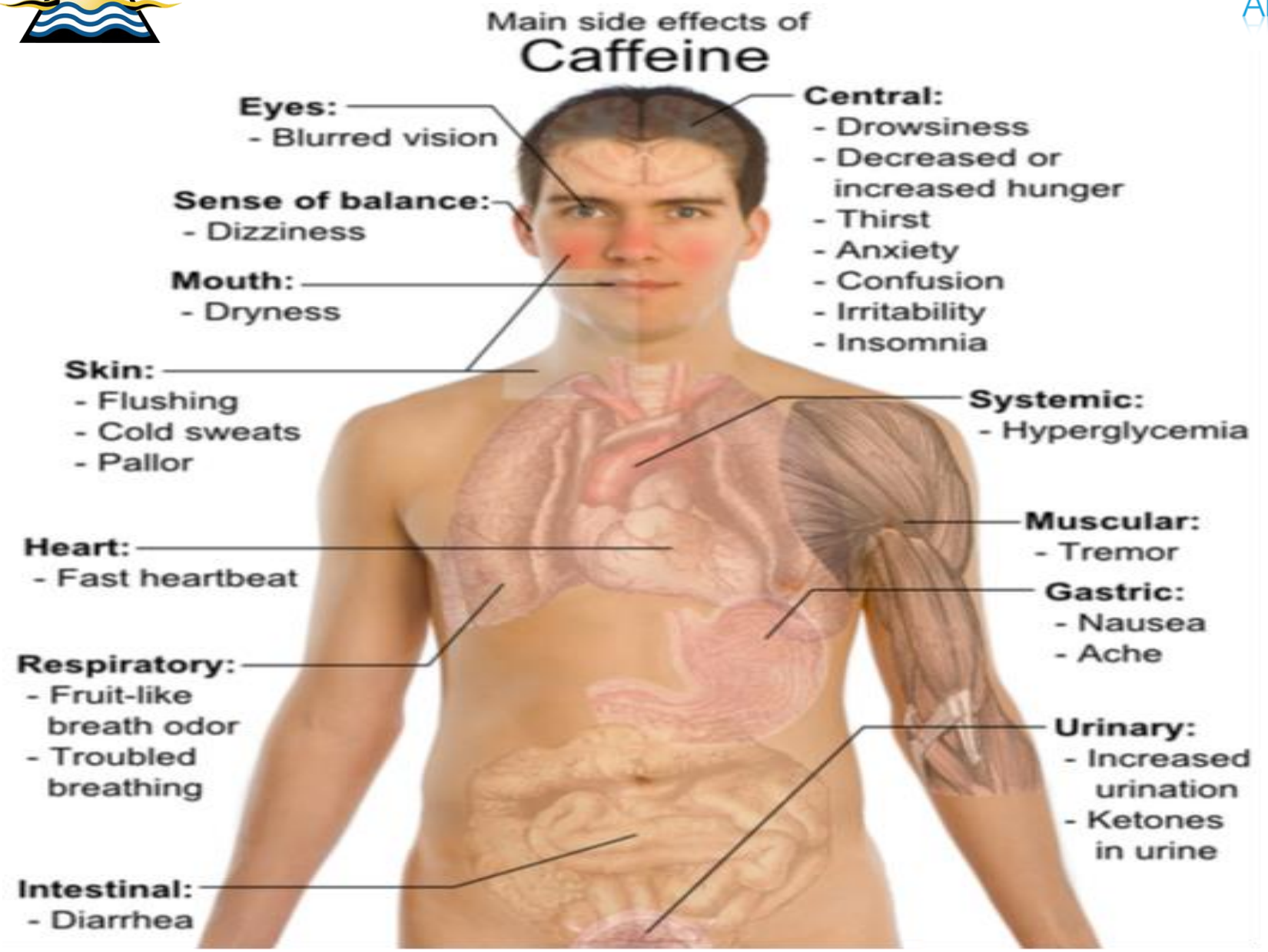


Figure 1: Physiological effects of caffeine.

WHAT DOES THIS MEAN?

If you have the slow – 1F allele of CYP1A2 – Coffee is not good for you – Avoid Caffeine intake

If you have the fast – 1A alleles of CYP1A2 – Coffee intake is good for you – Advise clients to drink coffee


Main side effects of
Caffeine
Eyes:
- Blurred vision
Sense of balance:
- Dizziness
Mouth:
- Dryness
Skin:
- Flushing
- Cold sweats
- Pallor
Heart:
- Fast heartbeat
Respiratory:
- Fruit-like breath odor
- Troubled breathing
Intestinal:
- Diarrhea
Central:
- Drowsiness
- Decreased or increased hunger
- Thirst
- Anxiety
- Confusion
- Irritability
- Insomnia
Systemic:
- Hyperglycemia
Muscular:
- Tremor
Gastric:
- Nausea
- Ache
Urinary:
- Increased urination
- Ketones in urine

Benefits of Caffeine

Parkinson's disease

- Researchers from the Harvard School of Public Health in Boston have concluded that regular caffeine consumption leads to a lower risk of developing Parkinson's by up to 80%.

- Caffeine reduces the amount of neurotransmitters produced by the brain, which may cause damage to surrounding brain tissue.

Gallstones

- Those who drink two to three cups of regular coffee a day have about a 20 percent lower risk of gallstones than non-drinkers.

o Caffeine may stimulate the gallbladder to contract, emptying stone-forming cholesterol and bile

Benefits of Caffeine

AnantLife

Mental Performance

- Improves alertness and reaction time

- Stimulates the central system as it simultaneously lowers blood sugar and increases the brain's demand for sugar. Resulting in a temporary lift.

Mood

- Increase in positive mood including an increased state of well-being, happiness, energy, arousal, alertness, and sociability.

Physical Performance

- Caffeine helps the body burn fat instead of carbohydrates, and it lowers levels of perceived pain.

- Improvements in aerobic physical endurance and anaerobic performance.

Benefits

Headache

- During a headache blood vessels dilate, but caffeine causes blood vessels to constrict relieving the pain.
- It is a mild analgesic.
- Helps the body absorb headache medications more quickly.
- Can makes pain relievers more effective by upregulating them.

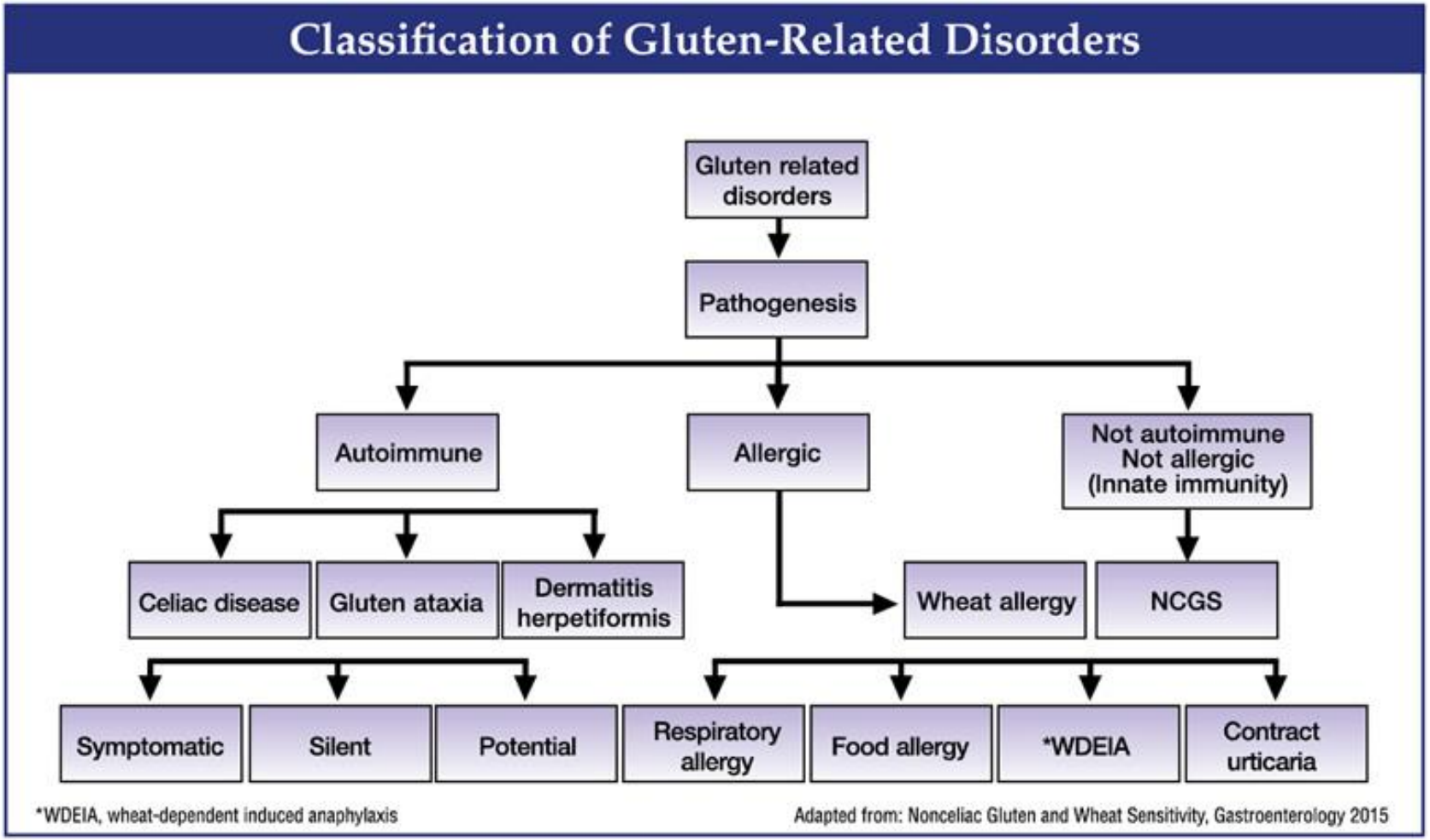
Heart Health

- Coffee is full of antioxidants.
- Moderate coffee intake can help prevent some cardiovascular problems.
- Women who drink two to three cups of coffee a day have a 25% lower risk of heart disease and an 18% lower risk of developing diseases other than cancer than non-coffee drinkers

GLUTEN SENSITIVITY

- Gluten is a protein found in many grains, including wheat, barley and rye. It's common in foods such as bread, pasta, pizza and cereal. Gluten provides no essential nutrients.
- Gluten sensitivity ie Gluten intolerance
- Gluten intolerant individuals at a higher risk of Celiac Disease
- No compelling evidence that a gluten-free diet will improve health if you don't have celiac disease
- Gluten free diet NOT recommended for individuals not at risk of gluten intolerance – cardiovascular health

GLUTEN SENSITIVITY



GLUTEN RELATED DISORDERS PREVALENCE

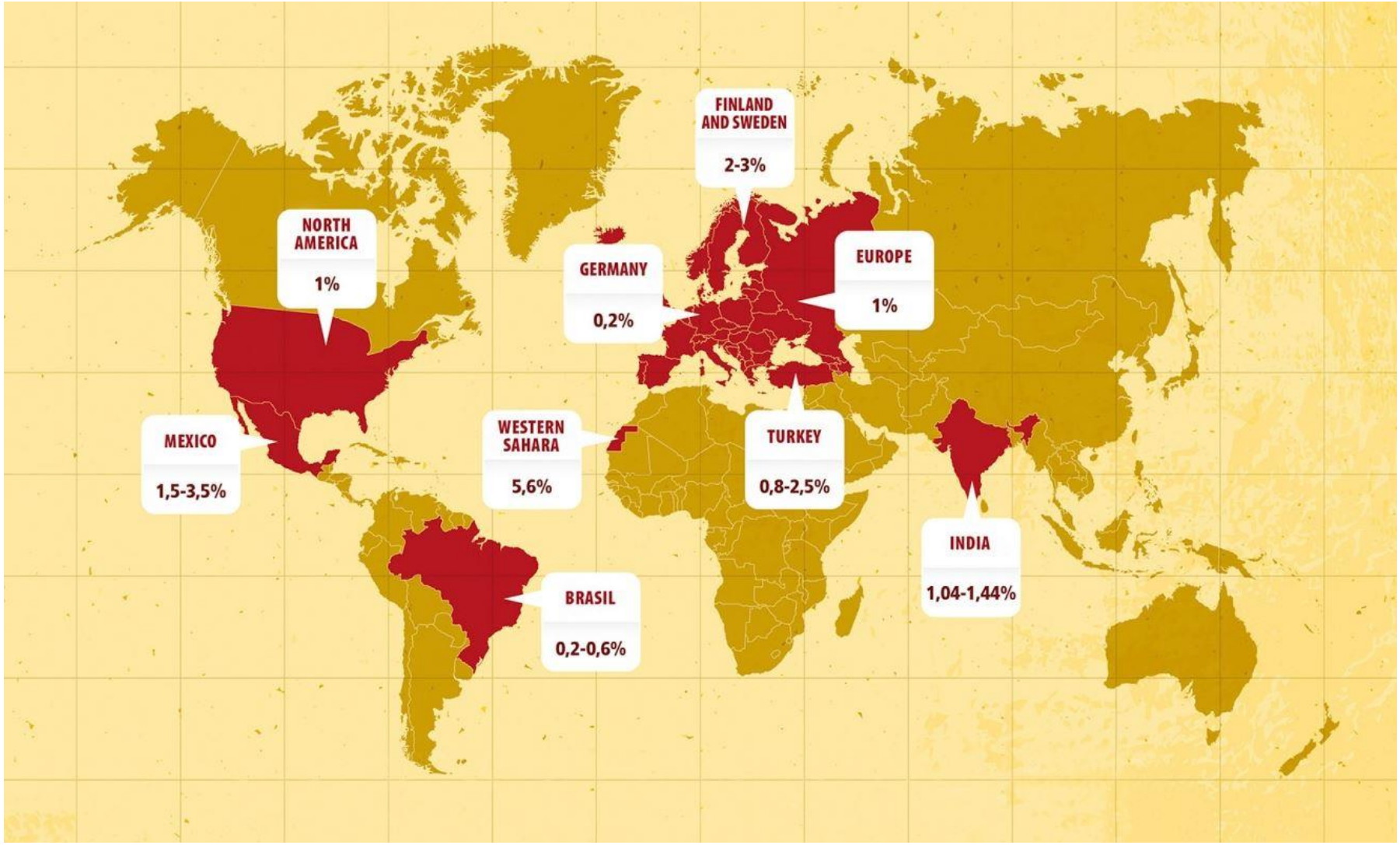
Against the Grain

A new study shows that people can have a reaction to gluten even if they don't have a wheat allergy or celiac disease.

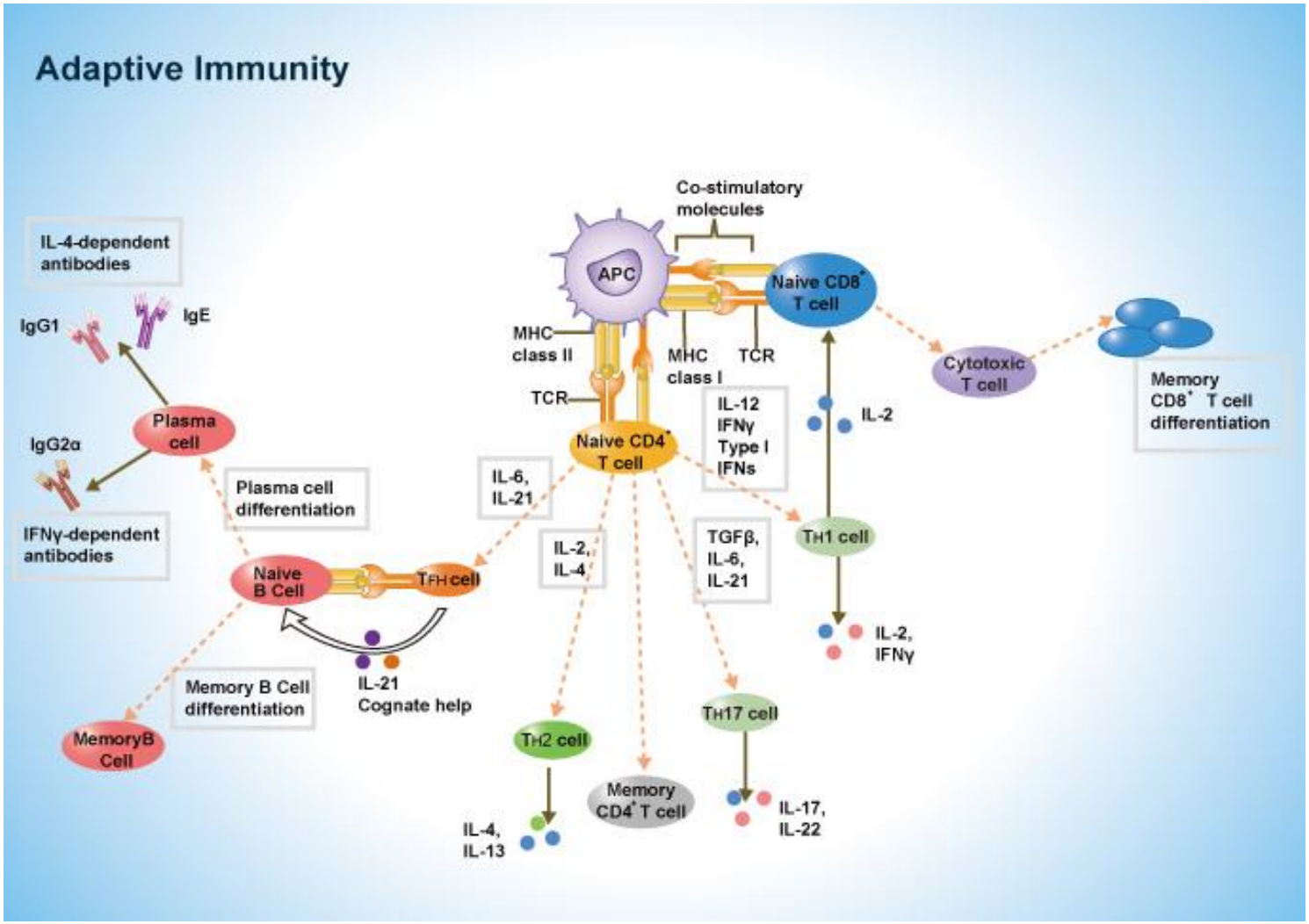
	Gluten Sensitivity	Wheat Allergy	Celiac Disease
Prevalence	6 % of U.S. population	Less than 1% of children; some adults after exercise	1% of U.S. population
Symptoms	Some stomach issues, also headaches, balance problems, many others	Hives, nasal congestion, nausea, anaphylaxis	Bloating, diarrhea, malnutrition, osteoporosis, cancer
Triggers	Gluten, amount unknown	Wheat proteins, but may cross react with other grains	Even small amounts of gluten
Treatment	Gluten-free diet, although small amounts may be tolerable	Avoid wheat products	Strict gluten-free diet

Source: WSJ reporting

PREVALENCE OF CELIAC DISEASE

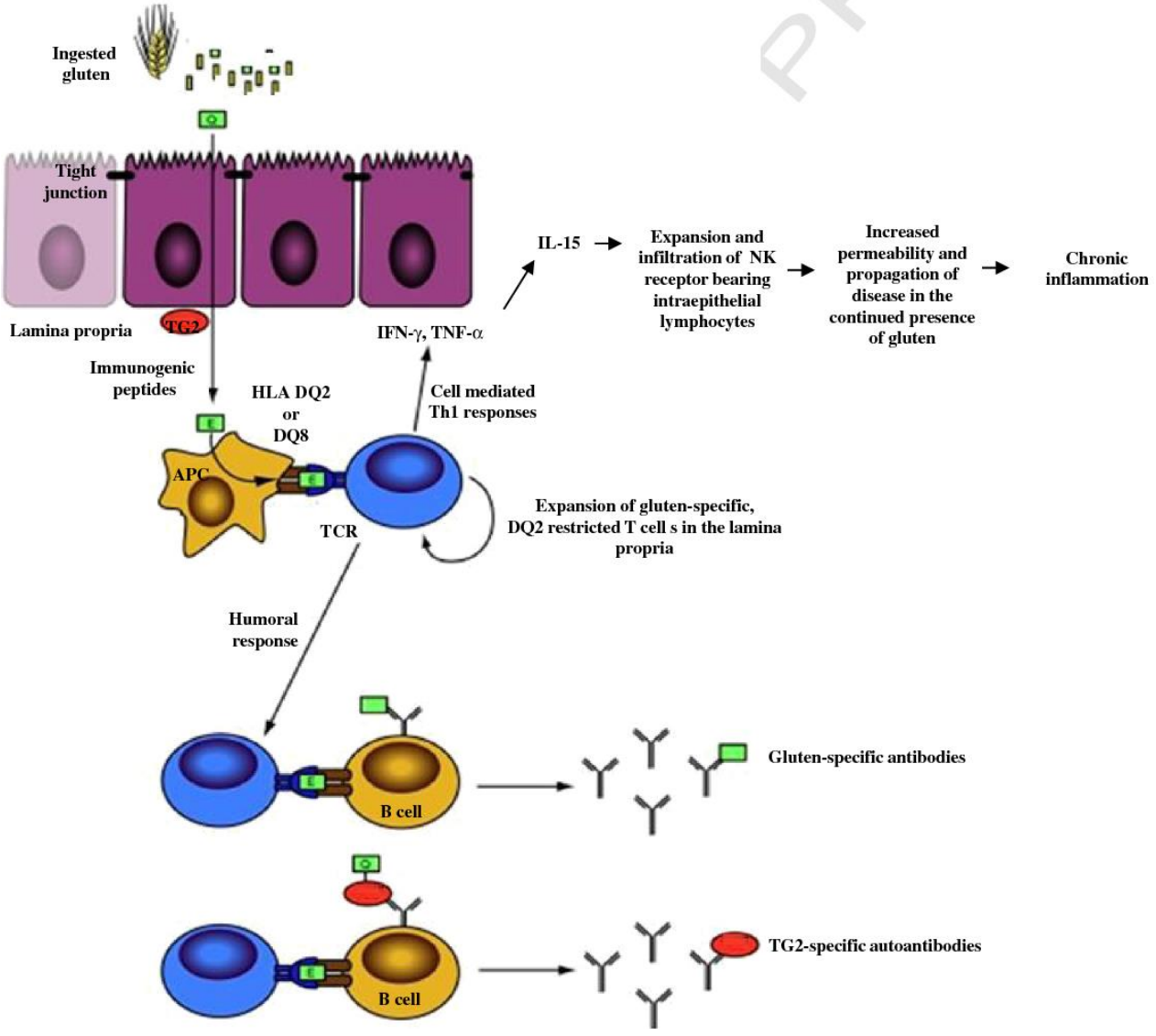


GLUTEN SENSITIVITY

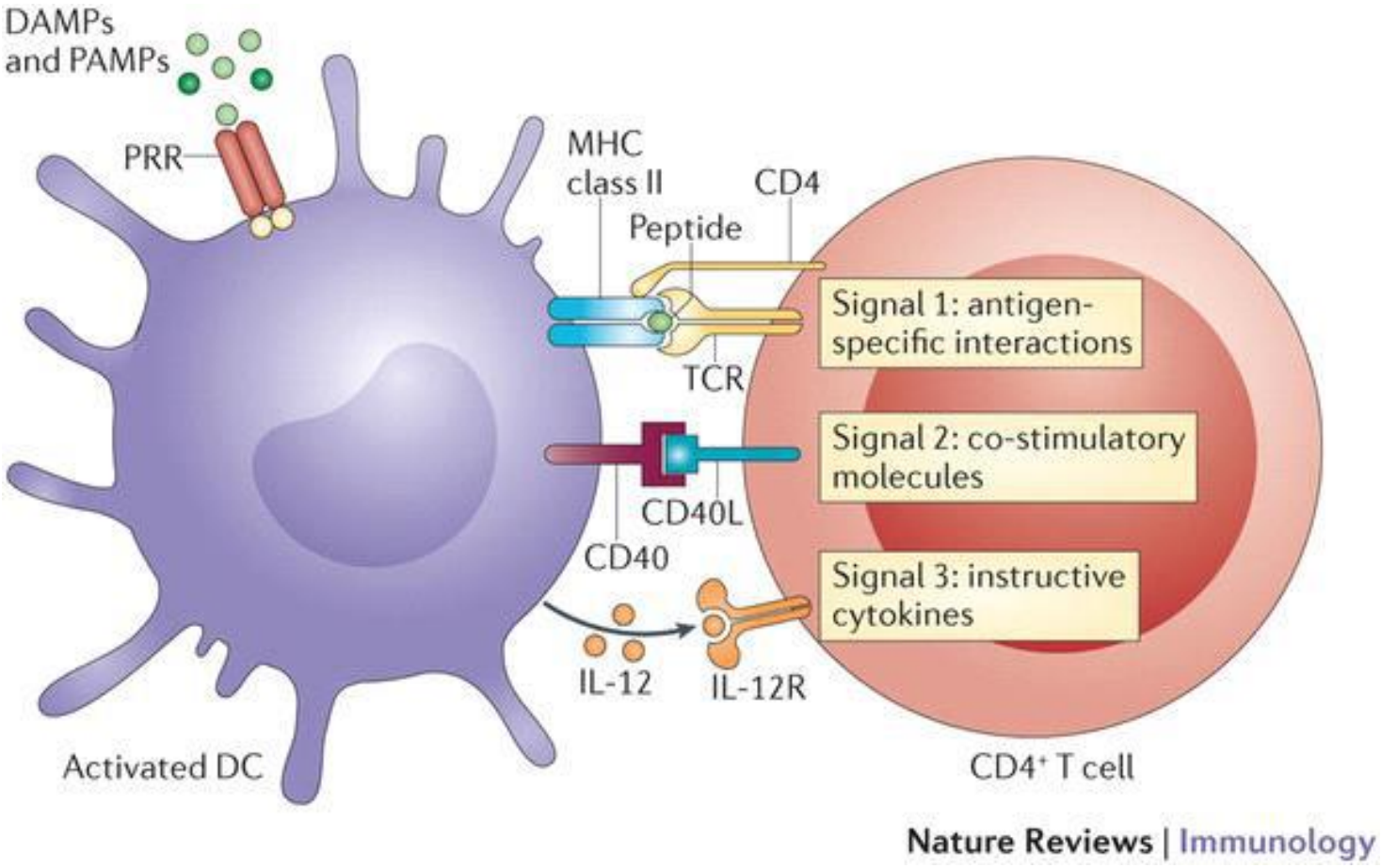


GLUTEN SENSITIVITY

drome, CD, ANA, and/or anti-thyroid antibodies positivity

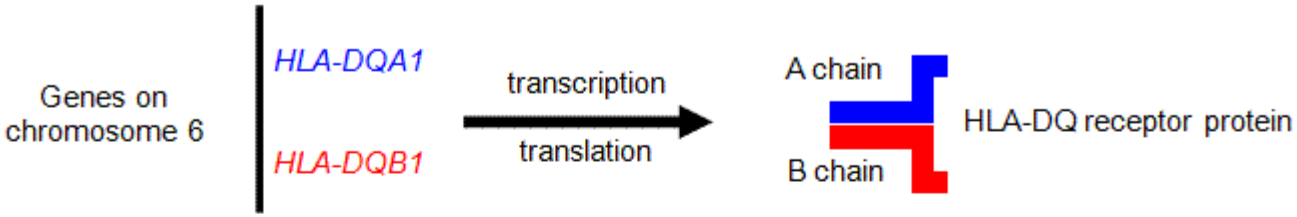


MHC MOLECULES AND GLUTEN INTOLERANCE



GLUTEN SENSITIVITY

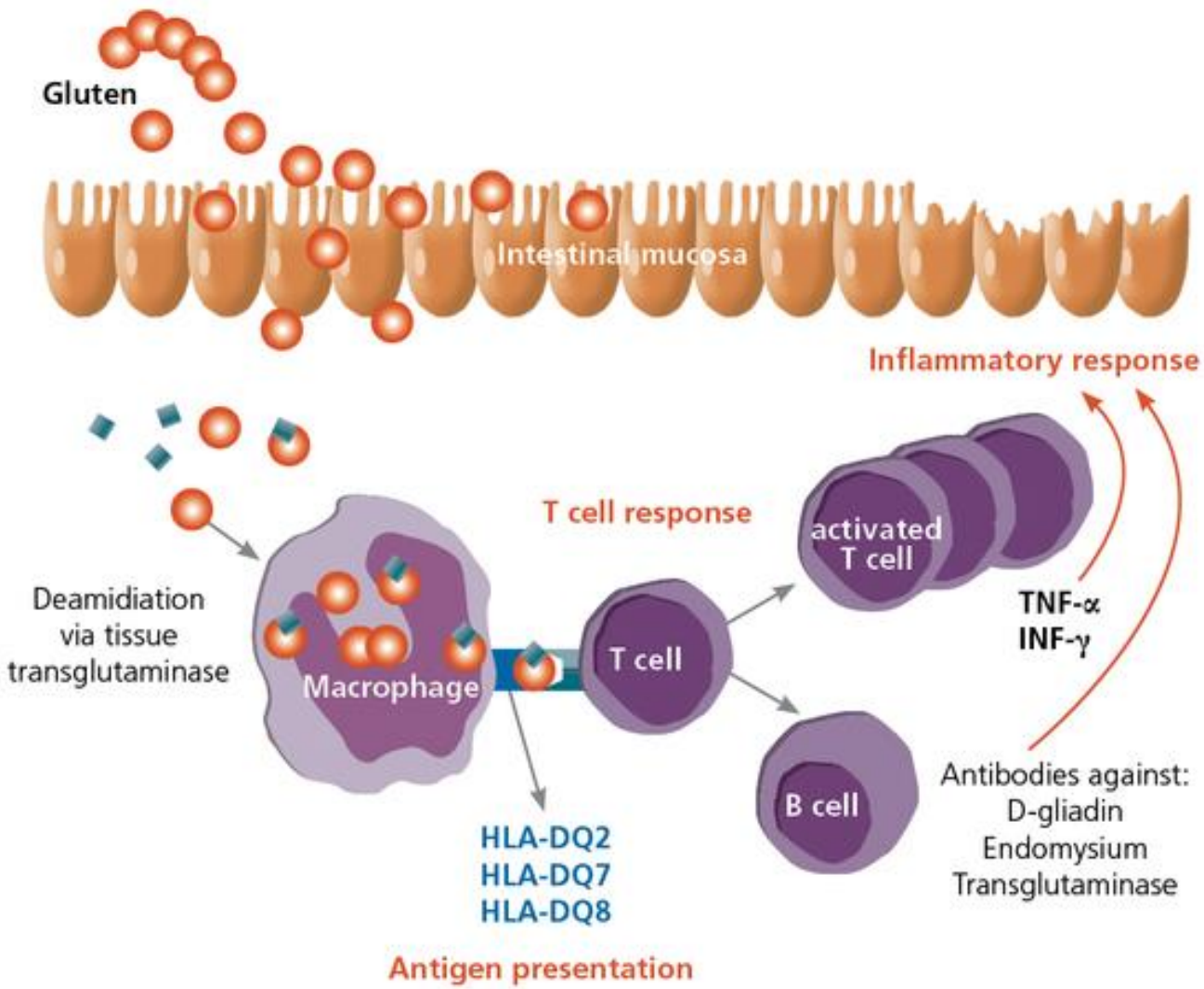
- **Genetics of HLA-DQ2 and DQ-8 governs risk of gluten sensitivity**



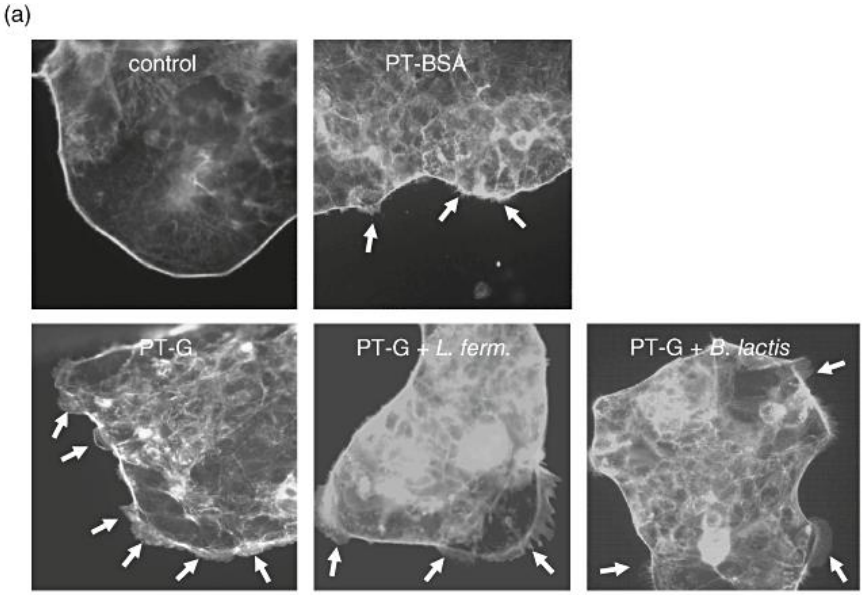
There are a range of possible HLA-DQ protein types, from DQ1 to DQ9, that are located on the surface of cells to act as receptors of antigen molecules.

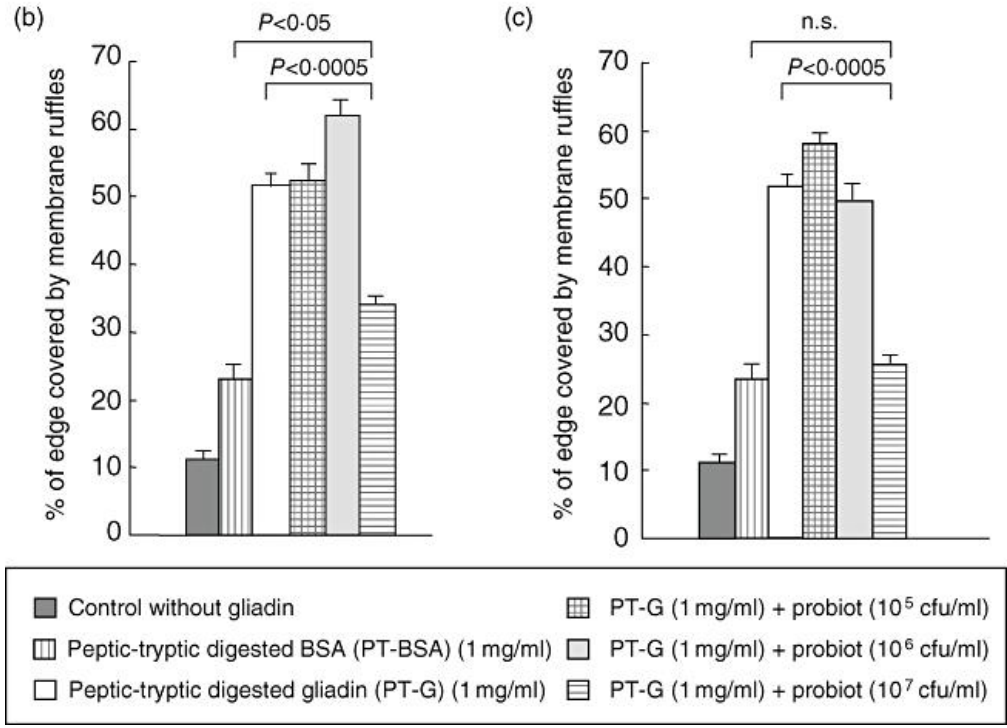
HLA-DQ2 and HLA-DQ8 bind gluten peptide fragment more strongly and can trigger an immune response more easily

GLUTEN SENSITIVITY



PROBIOTICS CAN REPRESS EFFECTS OF GLUTEN





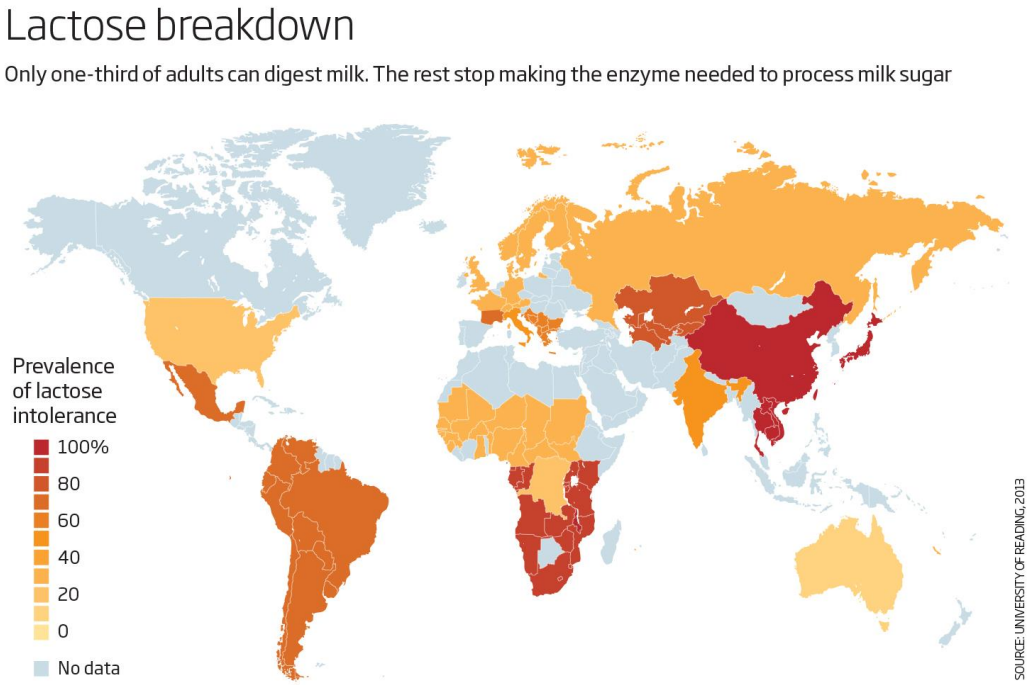
Lindfors et al 2008

WHAT TO DO IF SOMEONE IS AT RISK?

- **If individual is non-celiac:**
  - Reduction in dietary gluten intake
  - Incorporation of probiotics and prebiotics
- **If individual is celiac:**
  - Complete elimination of dietary gluten – gluten free diet
  - Probiotics and prebiotics

LACTOSE INTOLERANCE

- **Lactose intolerance, also called lactase deficiency or hypolactasia, is an inability to digest and metabolise lactose, a sugar found in milk.**



LACTOSE INTOLERANCE

- ***Hypolactasia*** **(*lactase nonpersistence, lactase restriction*): means that there is low lactase activity in the jejunal mucosa**

- ***Normolactasia*** **(*lactase persistence*): means that there is persistent lactase activity comparable to the neonatal period**

- ***Lactose maldigestion*** **and *lactose malabsorption* are terms to describe a poor lactose hydrolysing capacity without symptoms**

- ***Lactose intolerance*** **should only be used for a clinical entity, describing symptomatic lactose maldigestion (20% of hypolactasic individuals)**

CAUSES OF LACTOSE INTOLERANCE

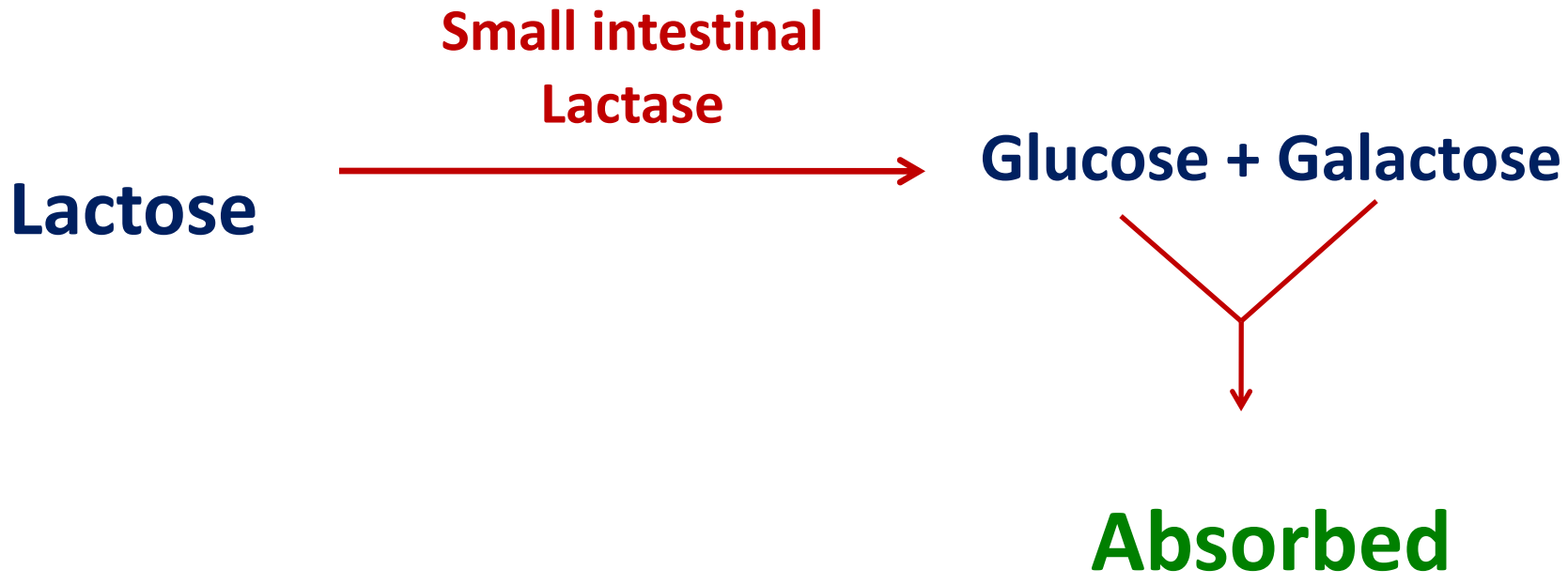
- 1-Congenital lactase deficiency
- because of a congenital absence (absent from birth) of lactase due to a mutation in the gene that is responsible for producing lactase. This is a very rare cause of lactase deficiency, and the symptoms of this type of lactase deficiency begin shortly after birth.

- 2-Primary lactose intolerance
- The most common cause of lactase deficiency is a decrease in the amount of lactase that occurs after childhood and persists into adulthood, referred to as adult-type hypolactasia. This decrease in lactase is genetically programmed, and the prevalence of this type of lactase deficiency in different ethnic groups is highly variable.

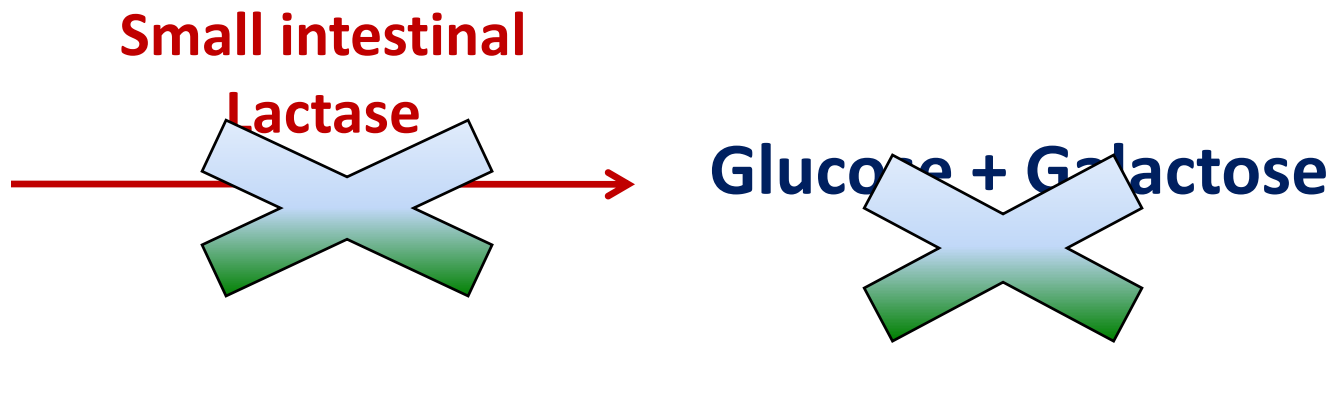
- 3-Secondary lactose intolerance
-
- This type of deficiency is due to diseases that destroy the lining of the small intestine along with the lactase. An example of such a disease is celiac sprue.

Normally

Disaccharides cannot be absorbed through the wall of the small intestine into the bloodstream



In lactose intolerance



In colon

Lactose —(Colonic bacteria secreting lactase)→ **Glucose + Galactose**

↓

Used and some splitted by these bacteria(fermentation)

↓

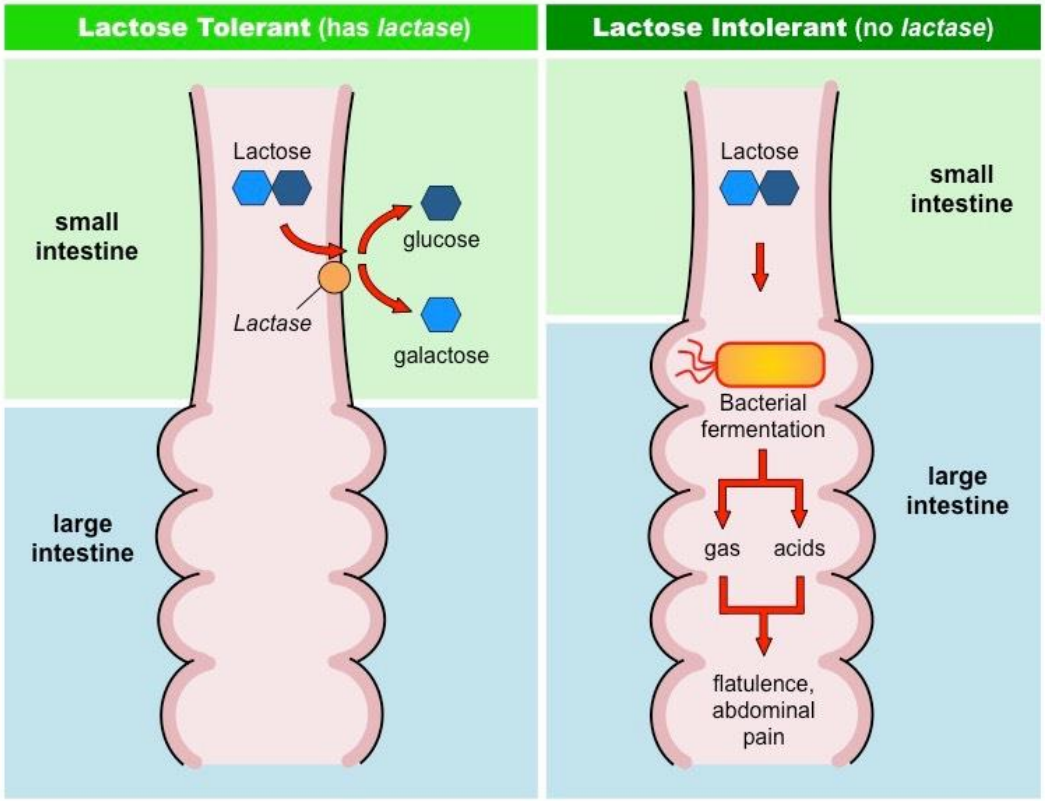
CO_2 gas+ Hydrogen gas + acids as lactic acid

- Most of the hydrogen is used up in the colon by other bacteria
- A small proportion is expelled → increased flatulence (passing gas)
- Some is absorbed from the colon and into the body → expelled by the lungs in the breath
- changed into methane gas by another type of colonic bacterium present in some people. These people will excrete only methane or both hydrogen and methane gas in their breath and flatus.

In colon

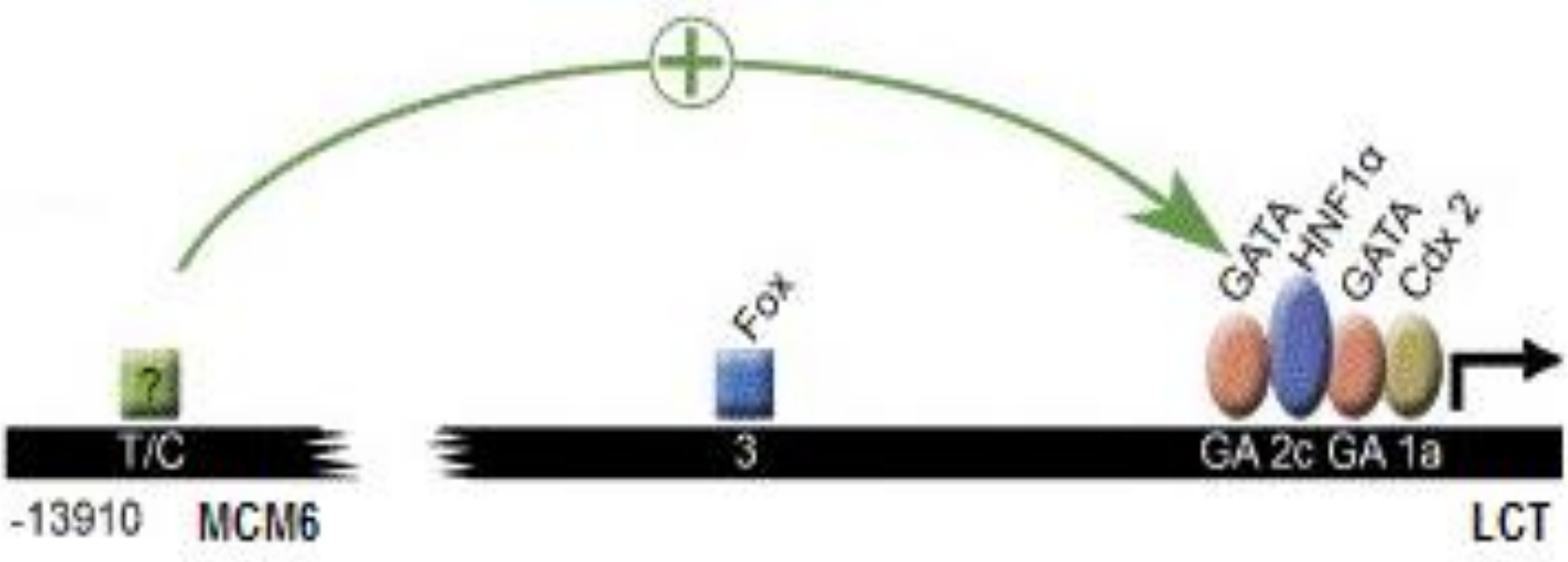
- **The copious amounts of gas** (a mixture of hydrogen, carbon dioxide, and methane), **may cause a range of abdominal symptoms, including** stomach cramps, nausea, bloating, acid reflux and flatulence.
- Not all of the lactose that reaches the colon is split and used by colonic bacteria. **The unsplit lactose in the colon and its fermentation products** draws water into the colon (by osmosis). This **leads to loose, diarrheal stools.**

LACTOSE INTOLERANCE



- Lactase enzyme is encoded by LCT gene
- MCM6 gene is found upstream of LCT and regulates LCT activity
- Individuals with T allele of MCM6 have lactase persistence
- Individuals with G allele of MCM6 do not have lactase persistence – higher risk of developing lactose intolerance

GENETICS OF LACTOSE INTOLERANCE



- **Individuals with T allele of MCM6 have lactase persistence**

- **Individuals with G allele of MCM6 do not have lactase persistence – higher risk of developing lactose intolerance**

WHAT TO DO IF SOMEONE IS AT RISK ?

- **Minimize consumption of lactose-rich dairy products, especially milk. Individuals vary quite a lot in how restrictive they have to be. Those that must severely restrict consumption of dairy products should likely take calcium supplements in another form.**
- **Consume reduced-lactose products. Lactose can be removed from milk and other dairy foods, and such products are widely available**
- **Consume a lactase supplement along with dairy products. A number of liquid or tablet preparations of lactase are available that assist digestion when consumed in conjunction with milk and other lactose sources.**
- **There is no evidence for adaptive alteration of lactase expression. In other words, intolerant individuals cannot become tolerant by consuming small then increasing quantities of lactose.**

REVIEW

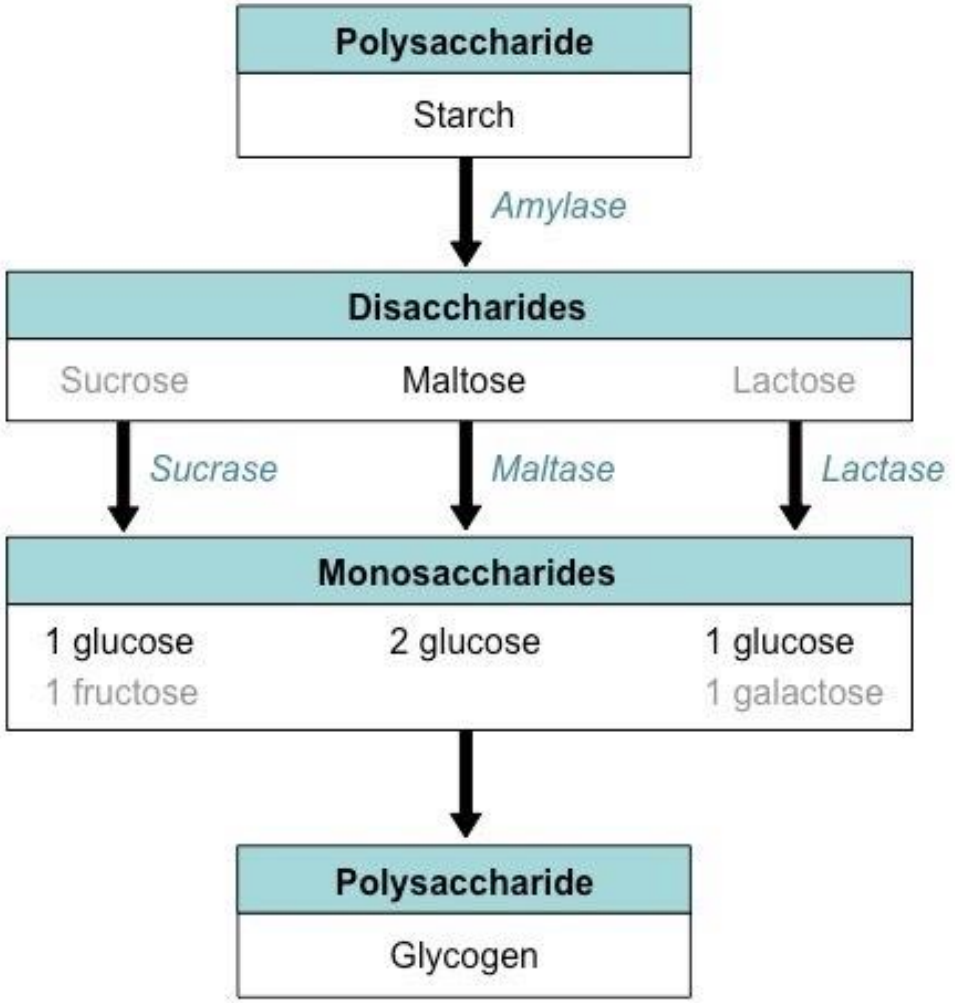
- Gluten intolerance
- HLA alleles
- Lactose intolerance
- Lactase
- MCM6

GENETICS AND DIET

- Starch intake and risk of insulin resistance
- Sodium intake and hypertension
- Appetite – snacking tendency
- Sugar preference
- Protein diet
- Dietary fiber and diabetes

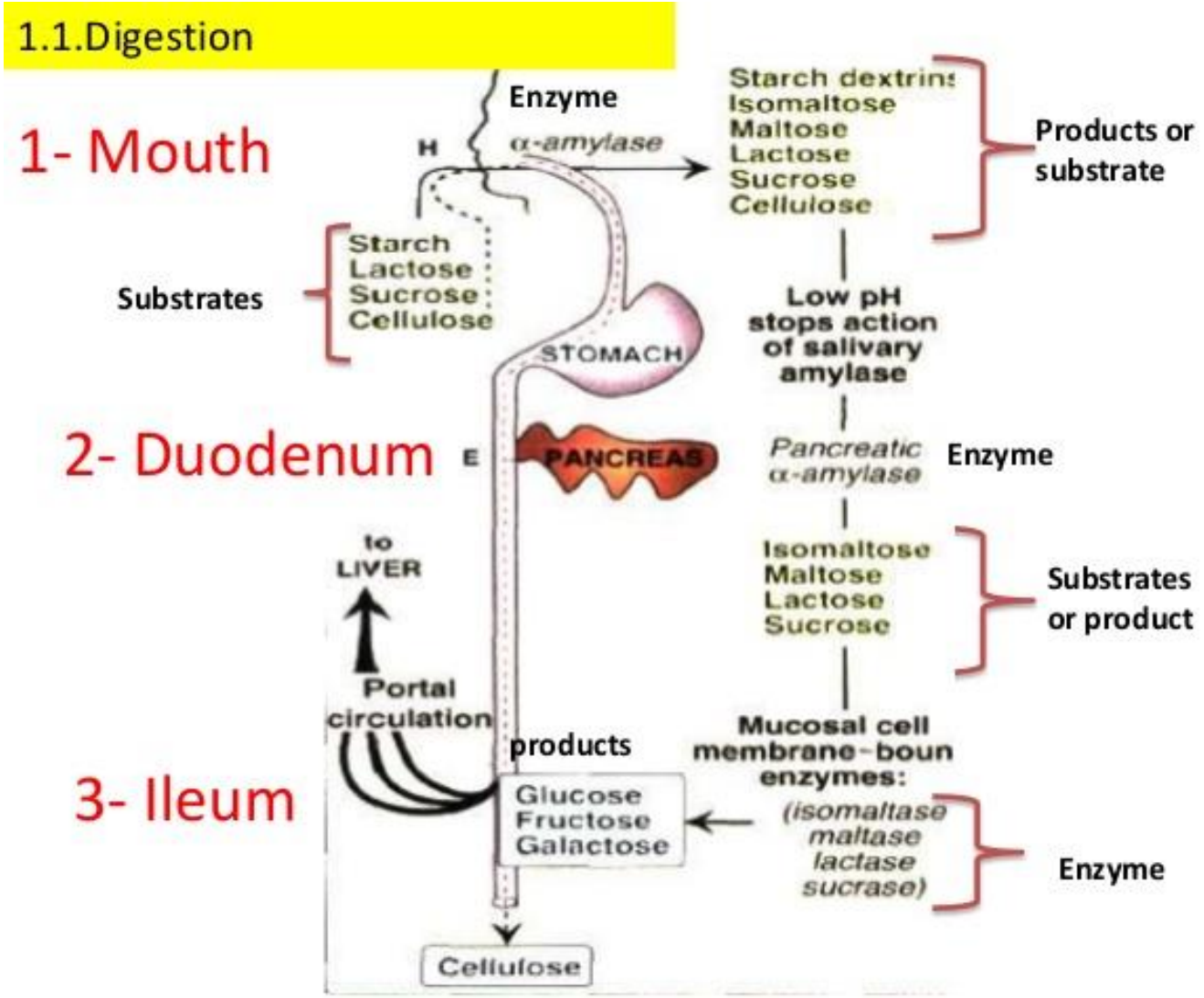
AMYLASE AND INSULIN RESISTANCE

- AMY1 encodes Alpha - amylase 1 - a key enzyme which breakdowns starch
- One of the key enzymes for digestion



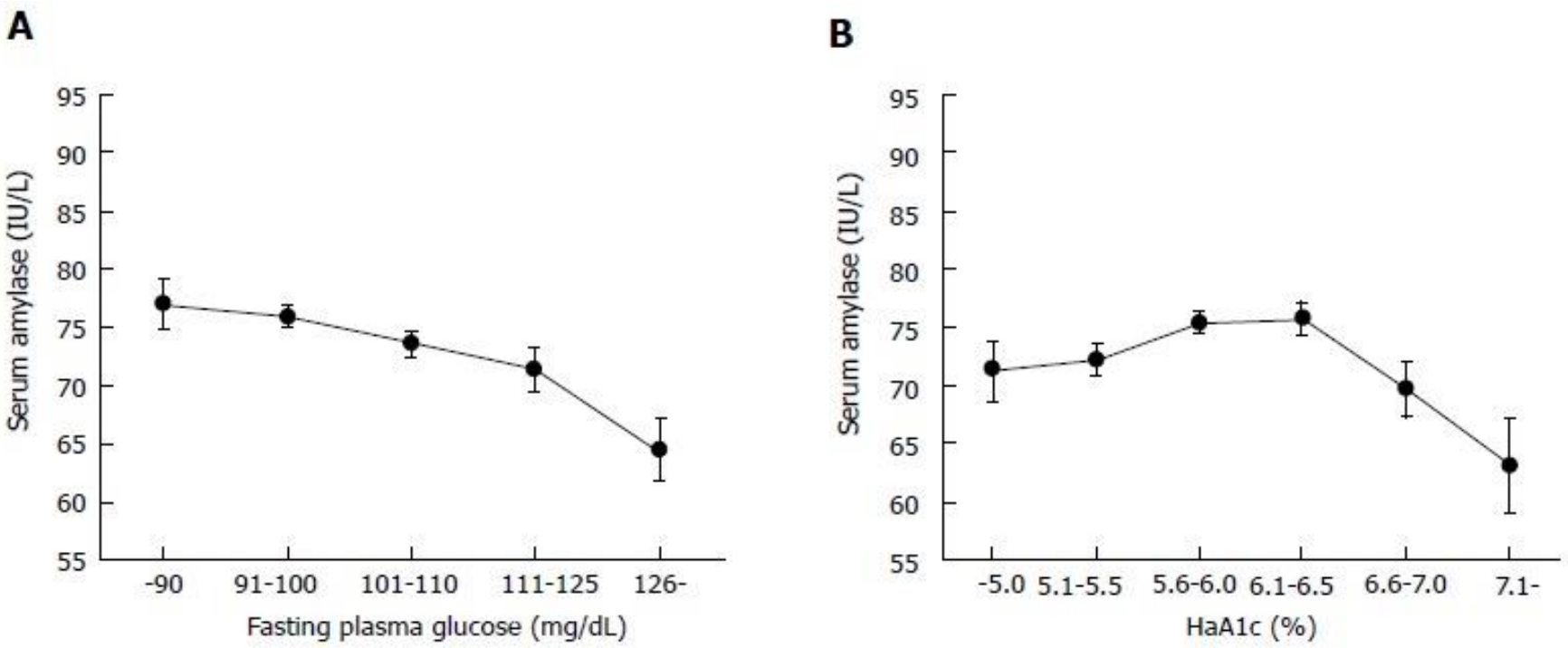
CARBOHYDRATE METABOLISM

1.1.Digestion



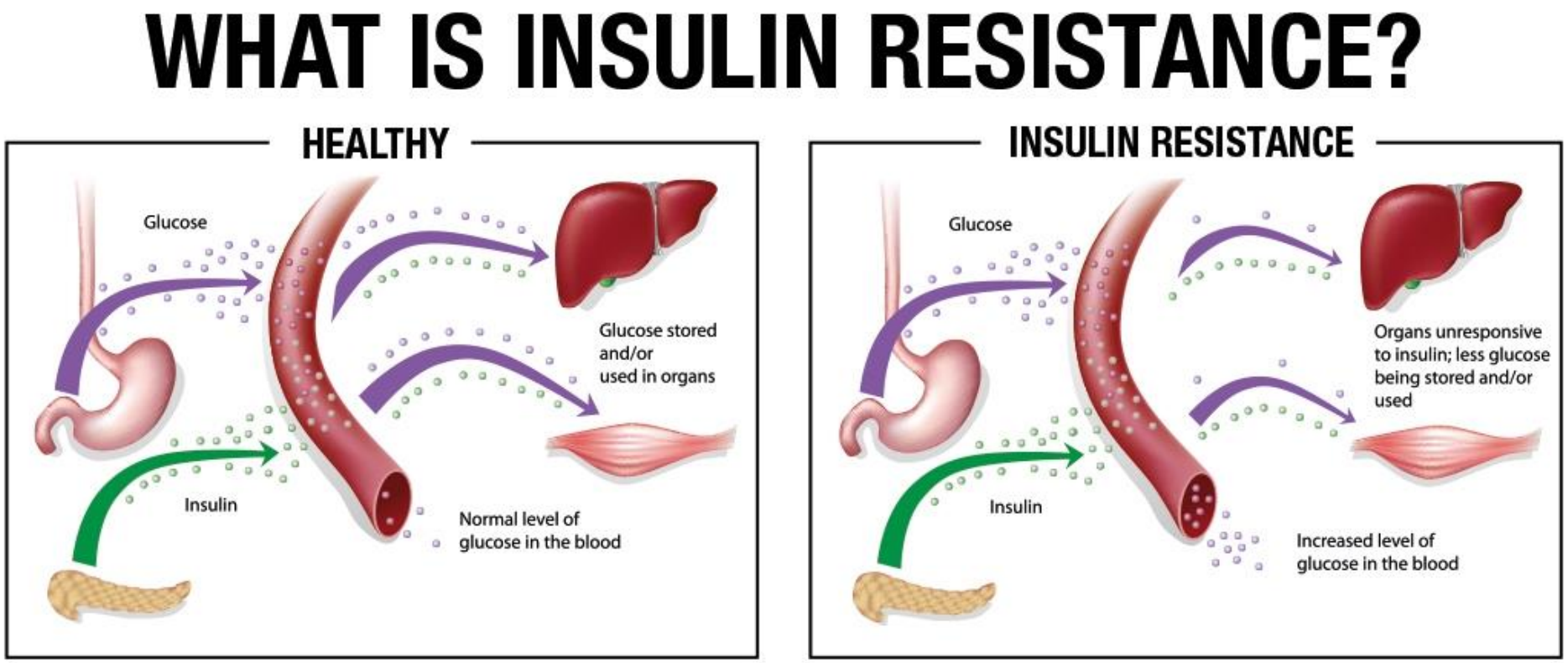
LOW AMYLASE ACTIVITY AND GLUCOSE LEVELS

Increased amylase correlates with better sugar control



Nakajima et al 2016

INSULIN RESISTANCE



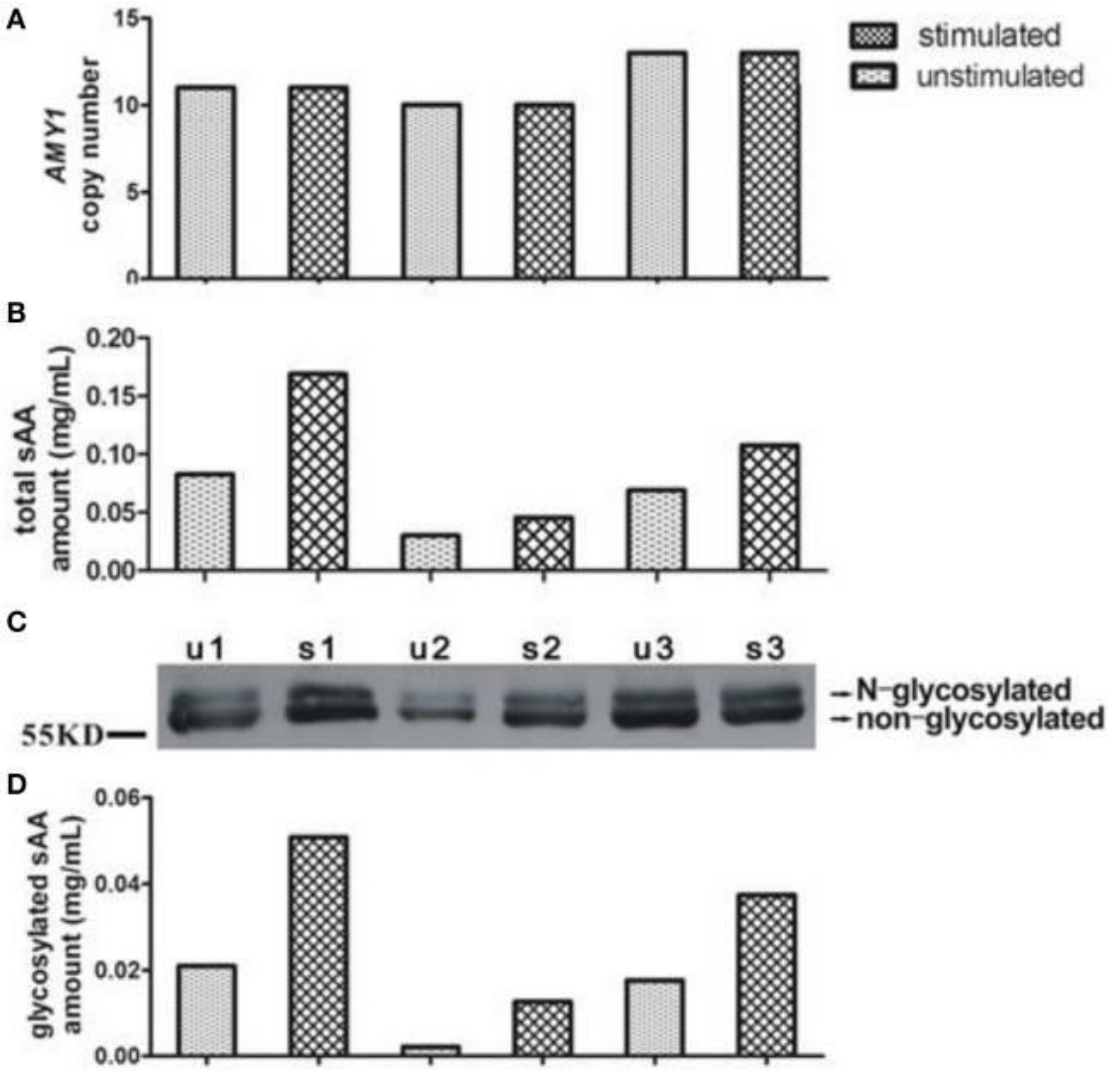
MUTATIONS IN AMY1

- AMY1 mutations that decrease AMY1 activity, increase the risk of insulin resistance due to reduced breakdown of starch

- WHAT TO DO WITH REDUCED AMY1 activity?

- Reduce carbohydrate intake
- Combine carbohydrates with low glycemic index food
- Citric Acid to induce saliva amylase
- Exercise >70% VO2max increases saliva amylase activity

CITRIC ACID CAN INDUCE SALIVA AMYLASE



Yang et al 2015

MUTATIONS IN AMY1

- AMY1 mutations that decrease AMY1 activity, increase the risk of insulin resistance due to reduced breakdown of starch
- Low Amylase activity associated with increased obesity risk
- Individuals with low AMY1 activity show increased predisposition to obesity, dysregulation in sugar control and insulin resistance – Metabolic disorder

SODIUM AND HYPERTENSION

2015-2020 Dietary Guidelines for Americans | Salt

Limit sodium intake to 2300 mg per day.

For those with prehypertension and hypertension, limit sodium intake to 1500 mg per day because reducing sodium intake can lower blood pressure.

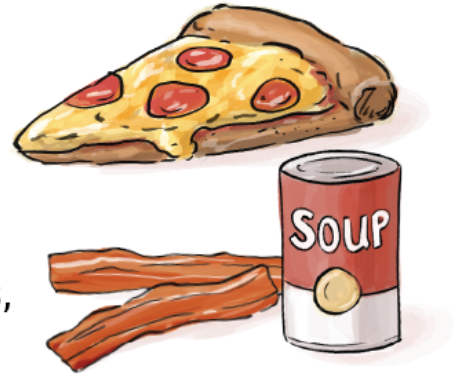
½ tsp of salt = 1200 mg of sodium

Biggest sources of sodium

Processed and ready-made foods

Restaurant and fast foods, including pizza, hamburgers, and sandwiches

Store-bought and processed foods, including deli meats, bacon, ham, sausage, frozen items, canned items, soups, sauces, and dressings

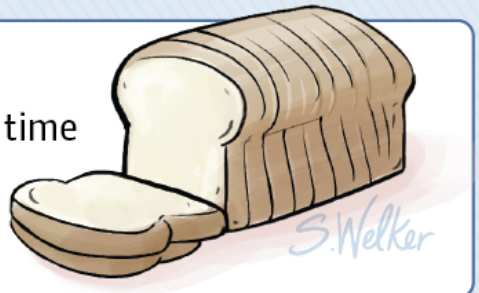


Hidden sources of sodium

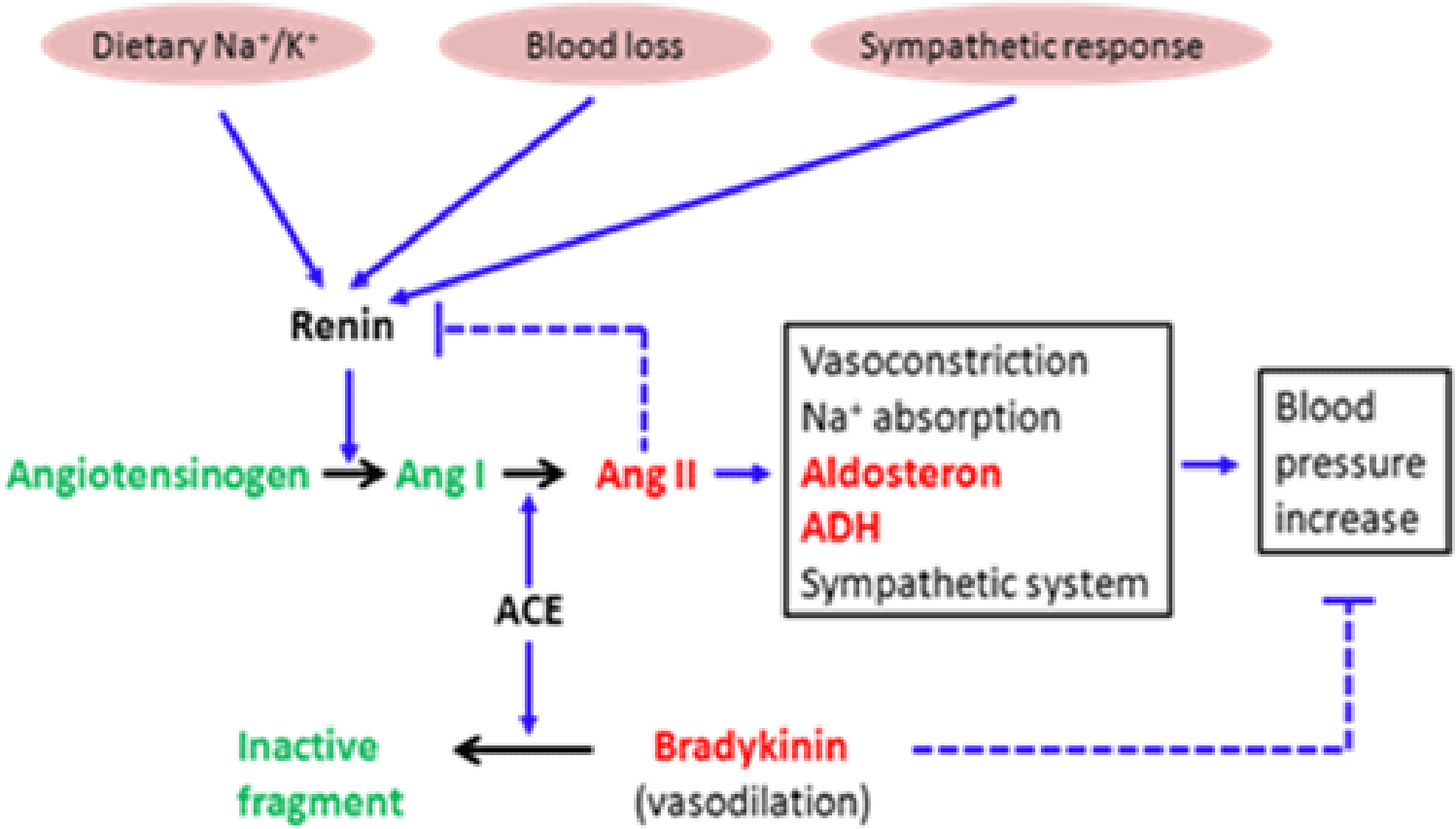
Shelf-stable products designed to last a long time

Bakery products, including sliced bread

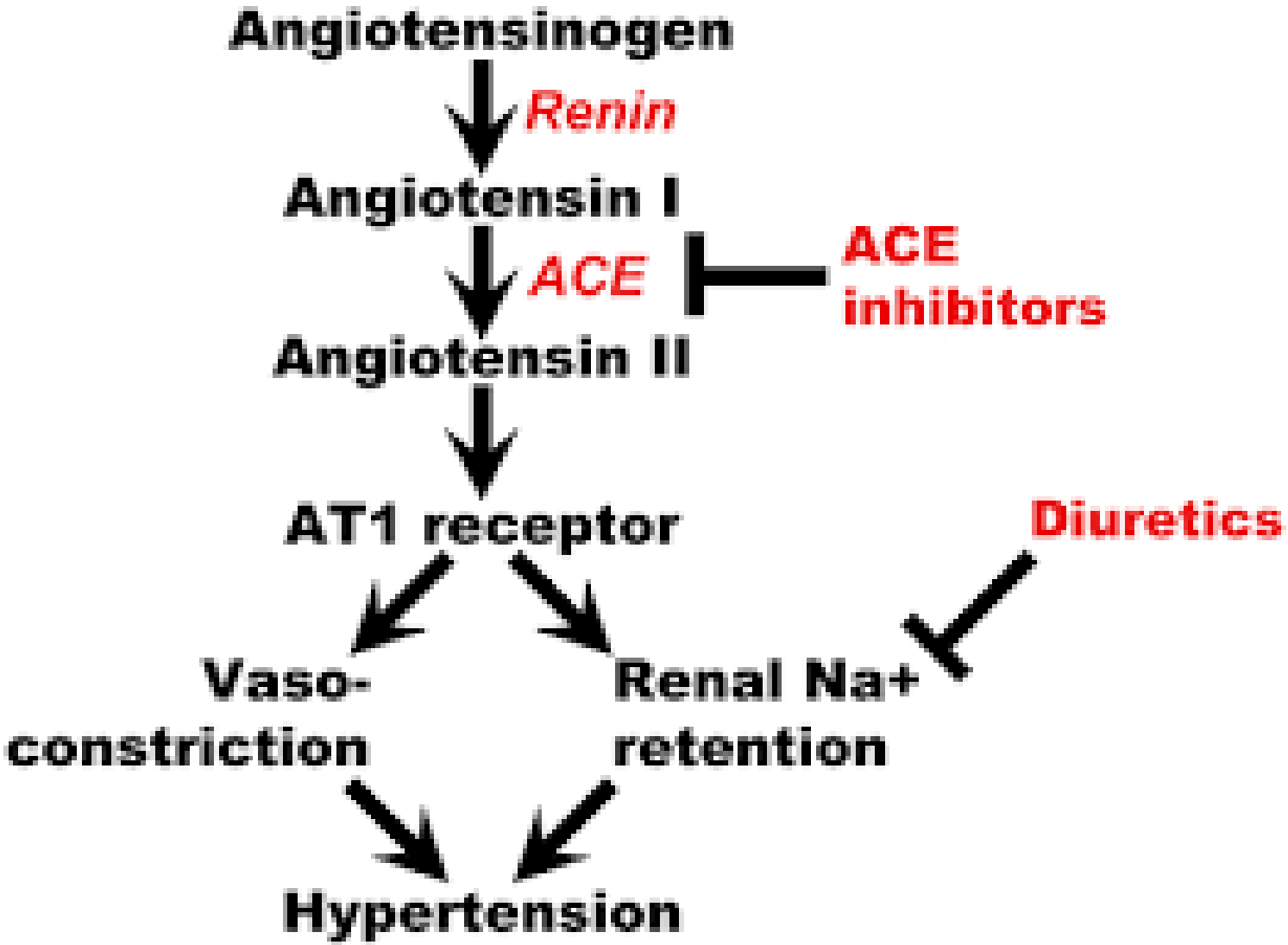
Cheese



ACE GENE – RAS SYSTEM



ACE INHIBITORS FOR HYPERTENSION



ACE GENETIC VARIATION

- There are two variants of the ACE gene in the human population: the I variant and the D variant.
- The I variant leads to a less active RAS system, a lower sensitivity to sodium, and a lower risk for hypertension.
- The D variant, which is generally considered the risk variant, leads to a more active RAS system due to higher ACE activity, a higher sensitivity to sodium, and a higher risk of hypertension.

ACE VARIATION AND SALT INTAKE

- Individuals with a salt intake ≥2.5 g/day and ID+DD genotypes had a 3.99-fold (p=0.004) higher risk of hypertension

ACE AT RISK GENOTYPE

- Reduce sodium intake
- Increase potassium intake
- Sodium transporters have increased activity with reduced potassium intake and decreased activity with increased potassium intake

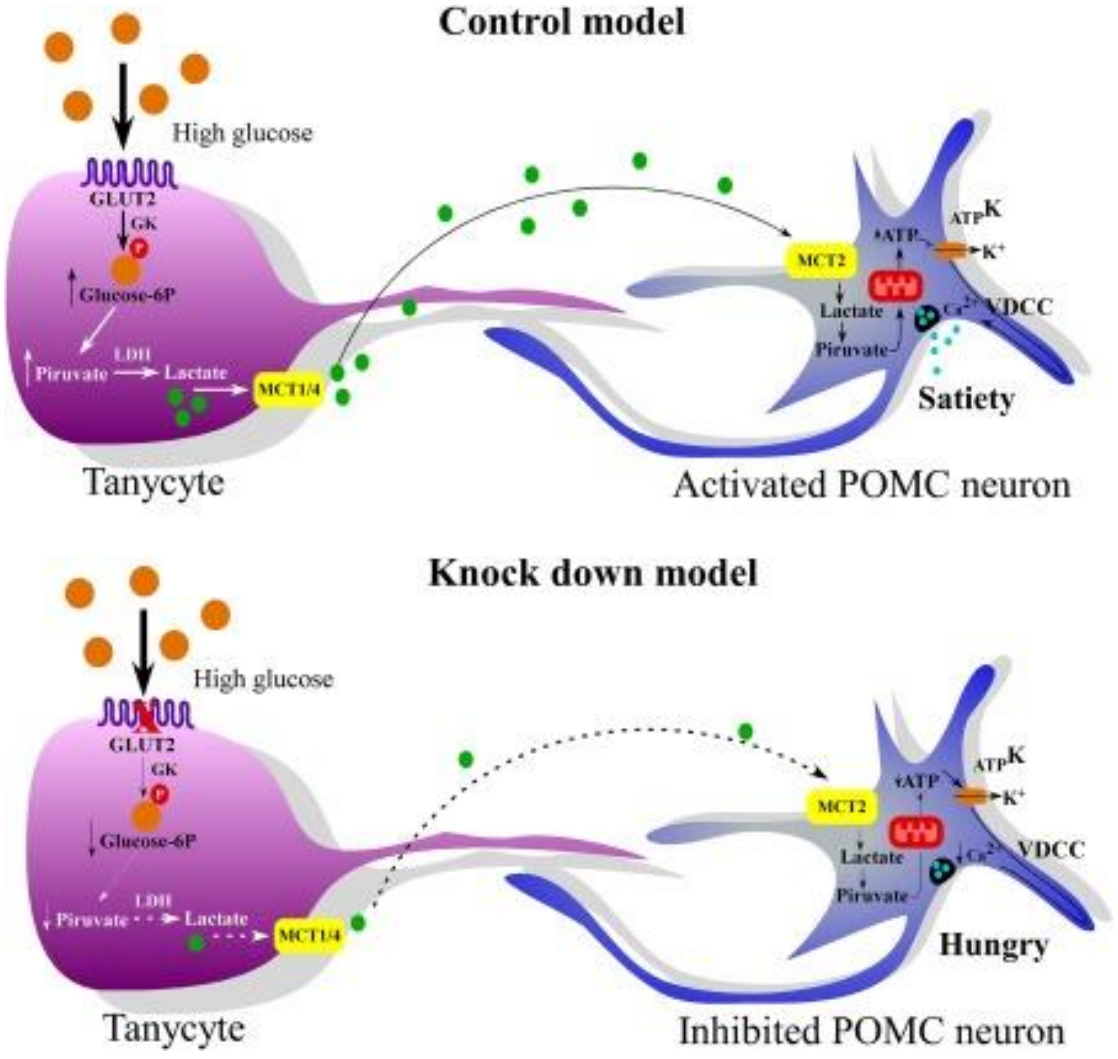
SUGAR PREFERENCE – GLUT2

- GLUT2 is a facilitative glucose transporter located in the plasma membrane of the liver, pancreatic, intestinal, kidney cells as well as in the portal and the hypothalamus areas.

- GLUT2 expression in hypothalamus has been shown to impact sugar craving.

SUGAR PREFERENCE & GLUT2 - MECHANISM

- Normal – GLUT2 binds sugar in tancycyte (specialized brain cells) and induces lactate release which activates POMC neurons and leads to sugar satiety
- Mutation – Reduced GLUT2 activity, POMC neurons not activated and there is craving for sugar – impaired sugar sensing



SUGAR PREFERENCE – GLUT2

- Threonine to isoleucine amino acid substitution at codon 110 (Thr110Ile) has been associated with risk of Type 2 diabetes, particularly conversion of impaired glucose clearance to diabetes
- Mutation may reduce GLUT2 activity
- The mutation likely results in impaired sensing of sugar which prevents satiety upon sugar intake
- Individuals carrying the mutation crave sugar

WHAT TO DO ?

- If someone is carrying Thr110Ile mutation, then:
  - Craving for sugar
  - Satiety is not easily achieved
  - Propensity for T2D
  - Diet planning with fruits that have low glycemic index
  - Fiber rich foods such as beans, legumes which aid in reaching satiety
  - Chia seeds

MC4R GENE AND APPETITE

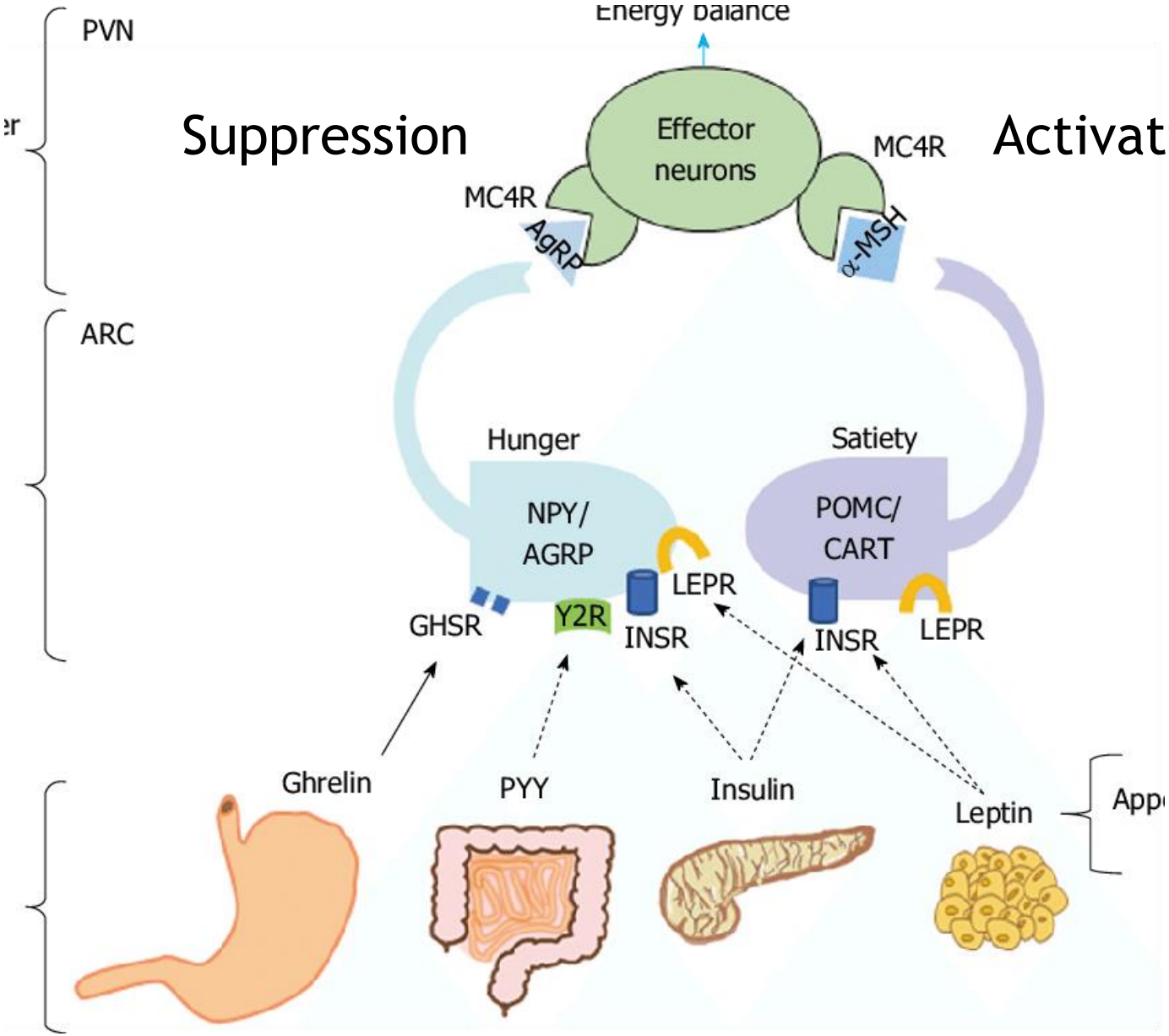
- Mutations in the MC4R gene account for 6-8% of obesity cases.
- A common variant of the MC4R gene, distributed in about 22% of the population, increases the risk for weight gain by causing increased appetite and decreased satiety.
- Calorie restriction through portion control and smart food choices is the best strategy for weight loss for people carrying this variant.

MC4R GENE AND APPETITE

- MC4R codes for a protein called melanocortin 4 receptor, which is mainly found in the hypothalamus of the brain, an area responsible for controlling appetite and satiety.

- Human body has many sensors for energy levels. When it senses high energy levels, it sends out “satiety signals” to activate the neurons through the melanocortin 4 receptor to alert the body that it’s full. When the body senses low energy levels, “hunger signals” activate the neurons, also through the melanocortin 4 receptor, to produce the feeling of hunger.

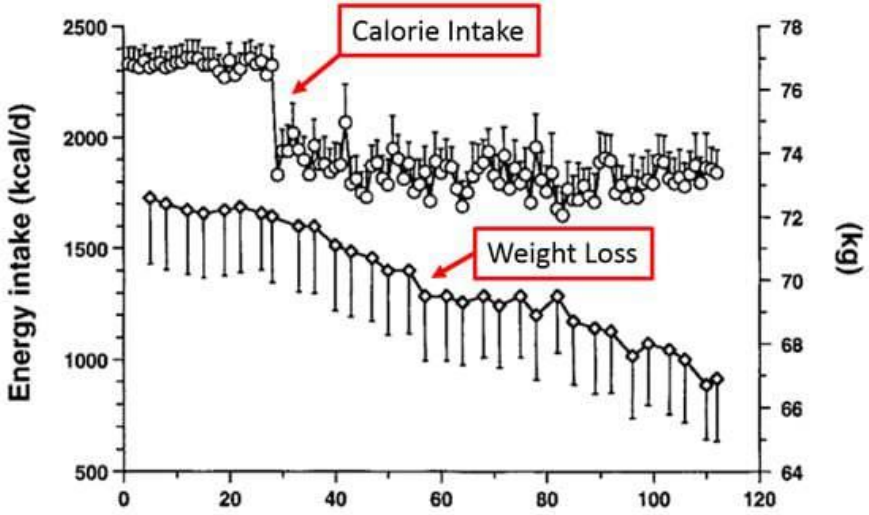
MC4R AND APPETITE

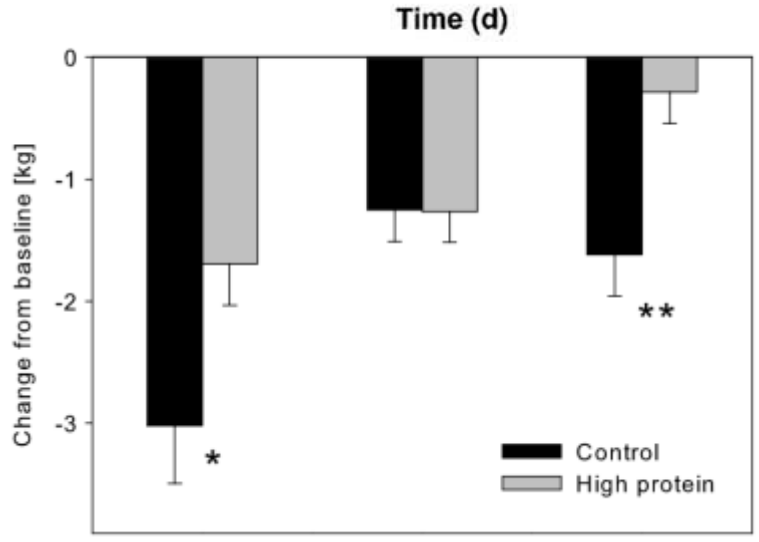


MC4R GENE AND APPETITE

- One common variant of the MC4R gene, carried by 22% of the general population, causes reduced MC4R protein level in the hypothalamus of the brain.
- Carriers of this variant have both increased appetite and decreased satiety. They tend to eat larger amounts of food, snack more frequently, and like to eat fatty foods. Studies have shown that each copy of the variant is responsible for a BMI (Body Mass Index) increase of 0.22 and an obesity risk increase of 8%.
- The most effective weight loss strategy for the variant carriers is calorie restriction, through portion control and smart food choice.

PROTEIN DIET AND GENETICS

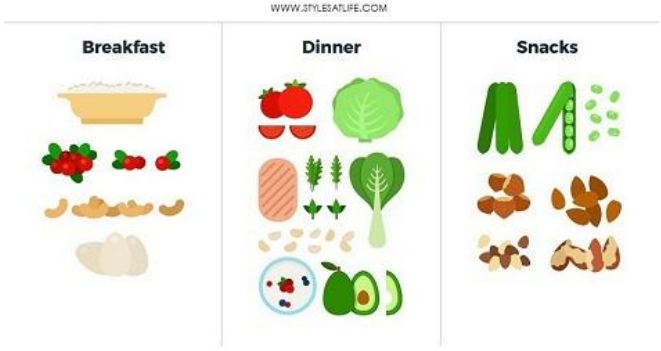




HIGH PROTEIN -DIET-

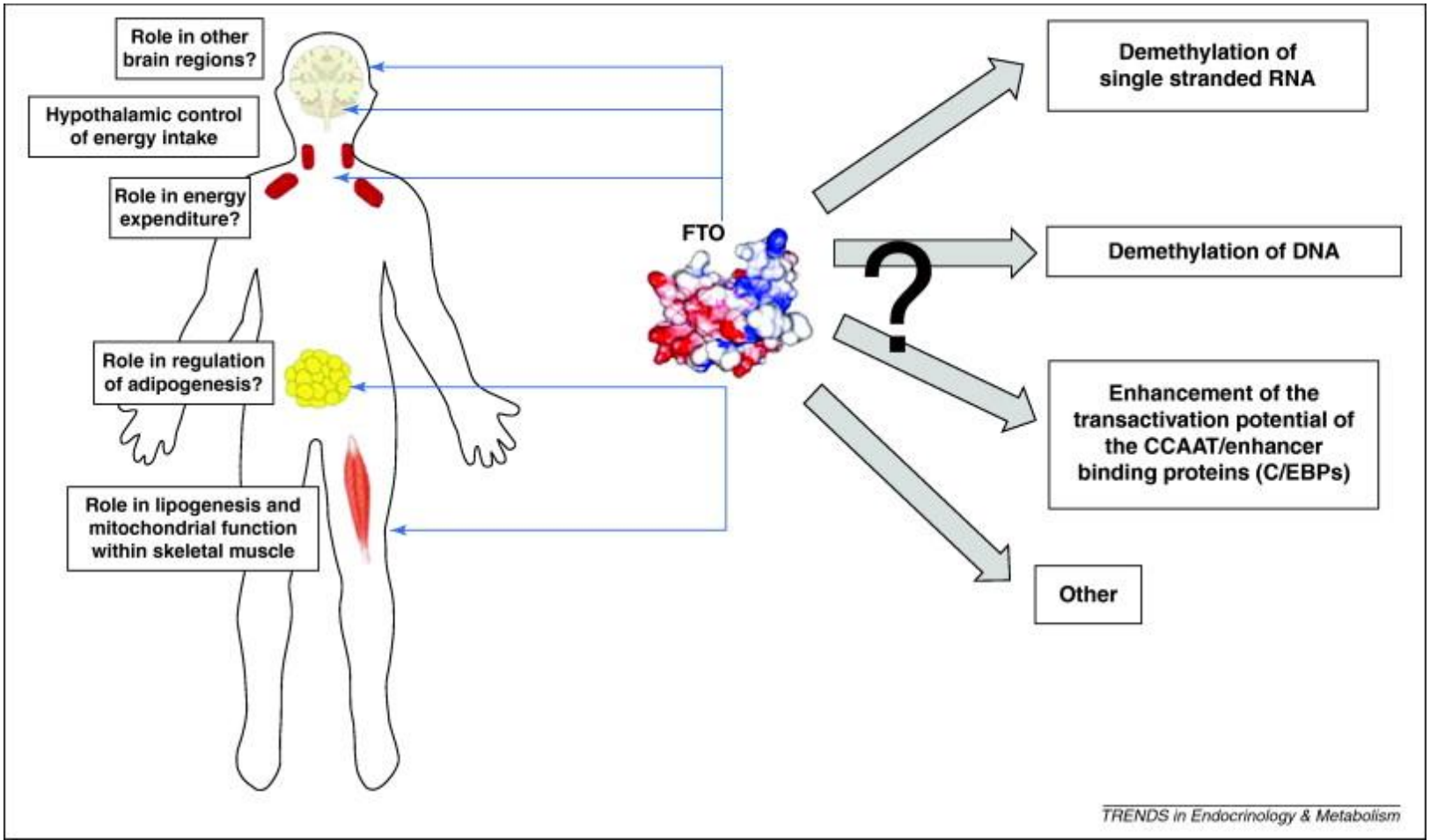
About

- ✓ No focus on calories, track and fat
- ✓ Enjoy food, no hunger
- ✓ Sugar cravings in the beginning.
- ✓ Quick initial weight loss
- ✓ Less gluten, happier stomach with less bloating

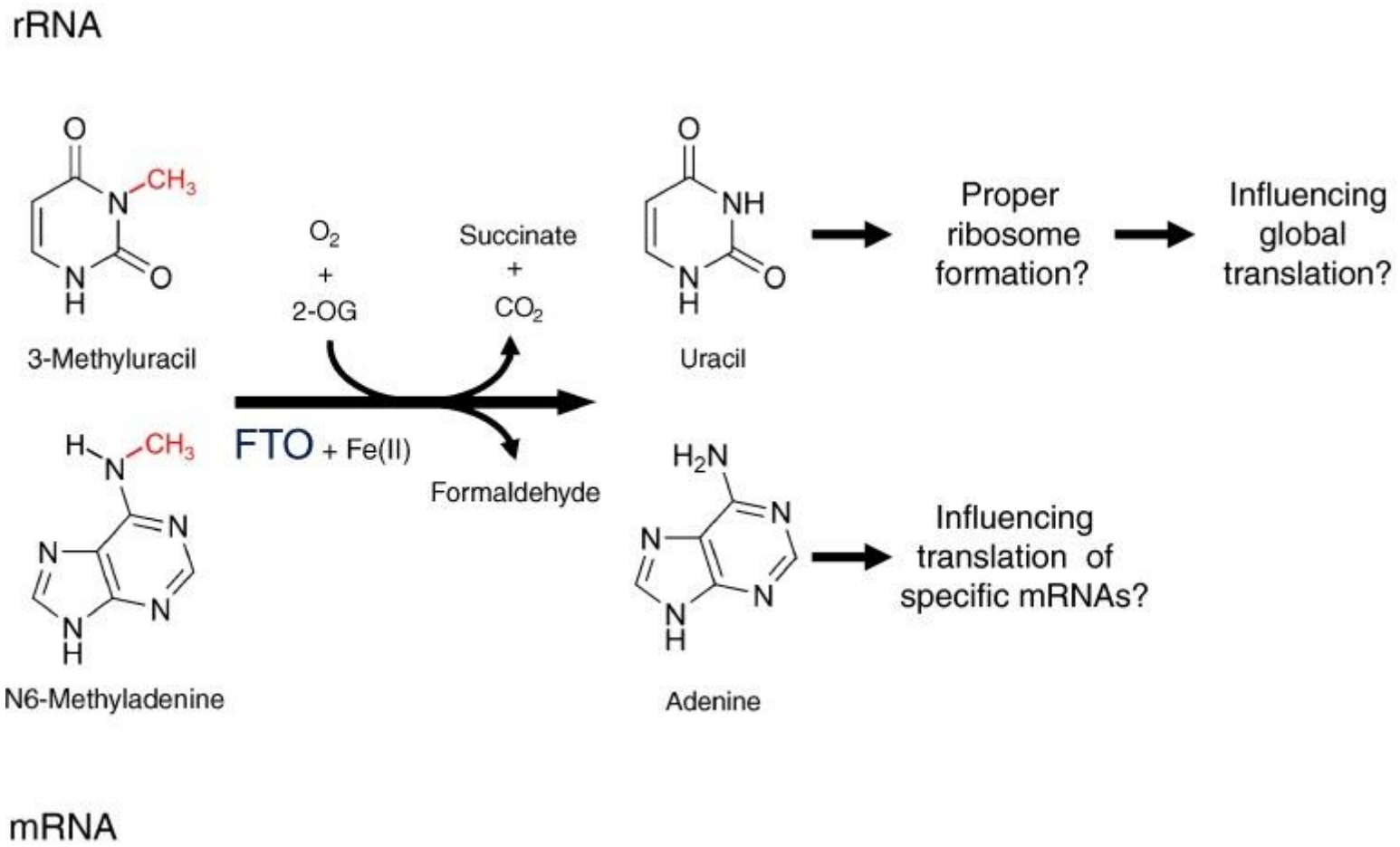


FTO – THE MISSING LINK

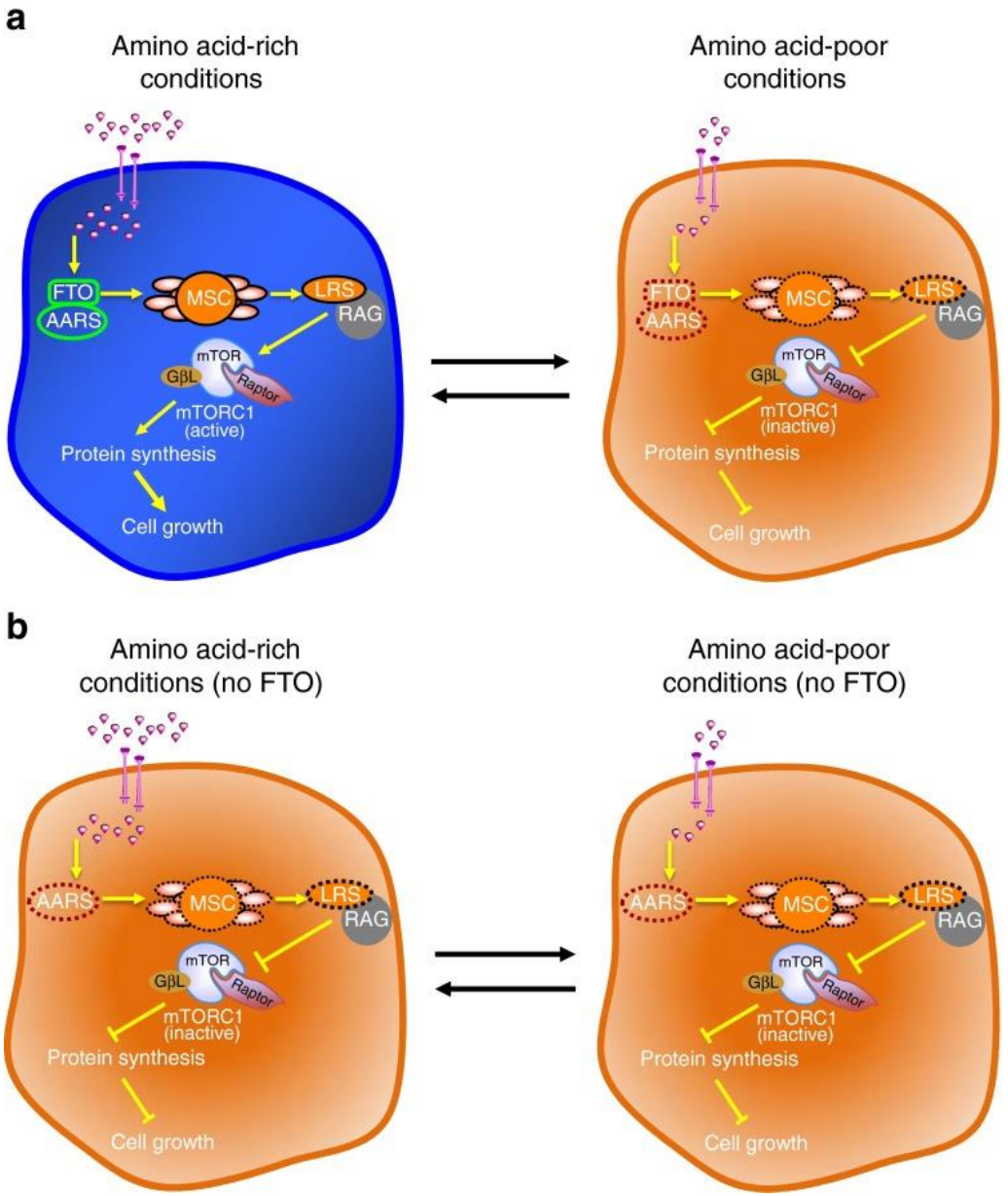
- FTO alpha-ketoglutarate dependent dioxygenase
- Inactive FTO - increased metabolism, less fat



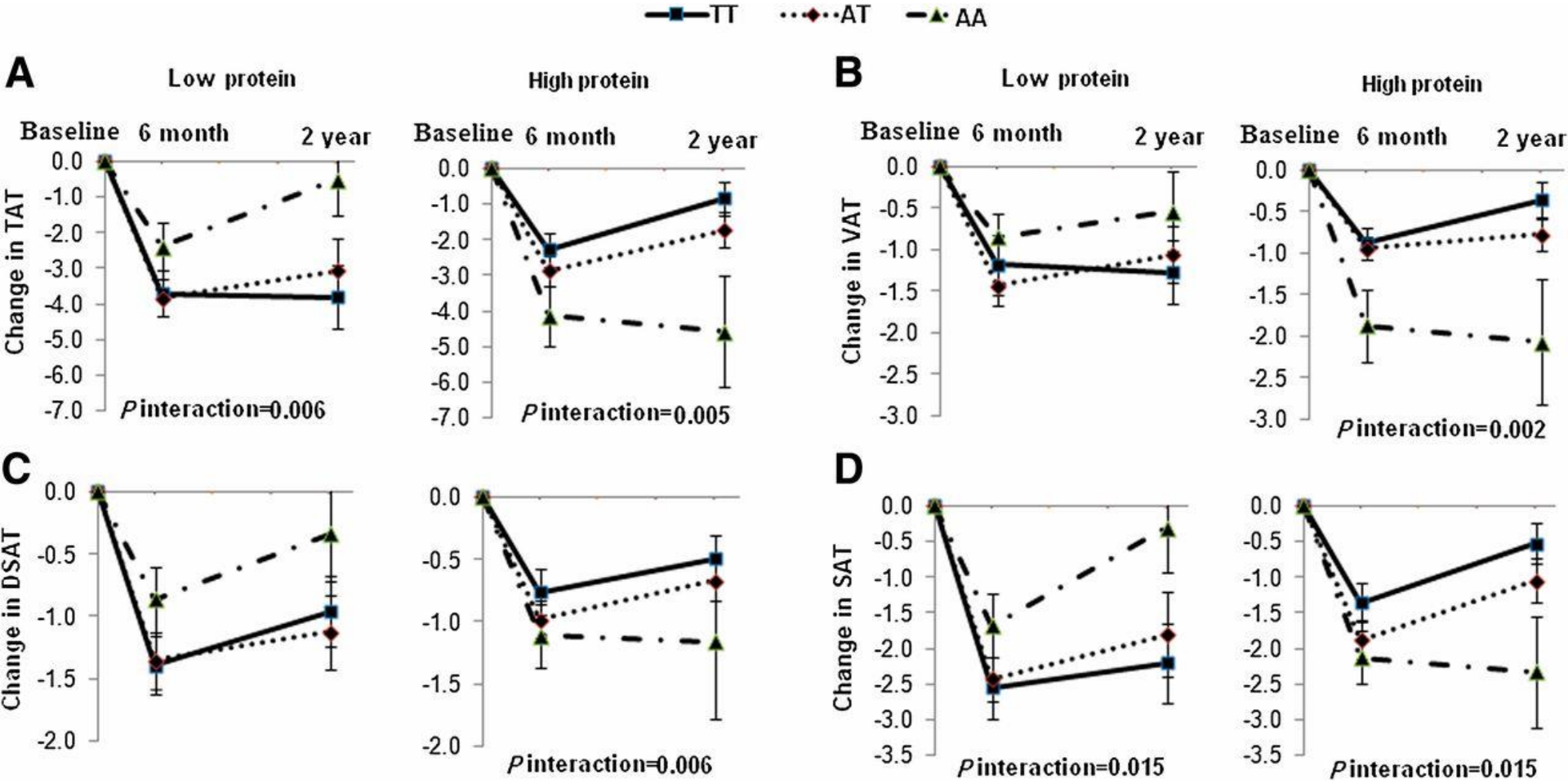
FTO – NUCLEIC ACID METHYLATION



FTO – AMINO ACID SENSOR



FTO GENOTYPE AND PROTEIN DIET



- total adipose tissue (TAT) volume, subcutaneous adipose tissue (SAT) volume at the trunk, and visceral adipose tissue (VAT), deep subcutaneous adipose tissue (DSAT)

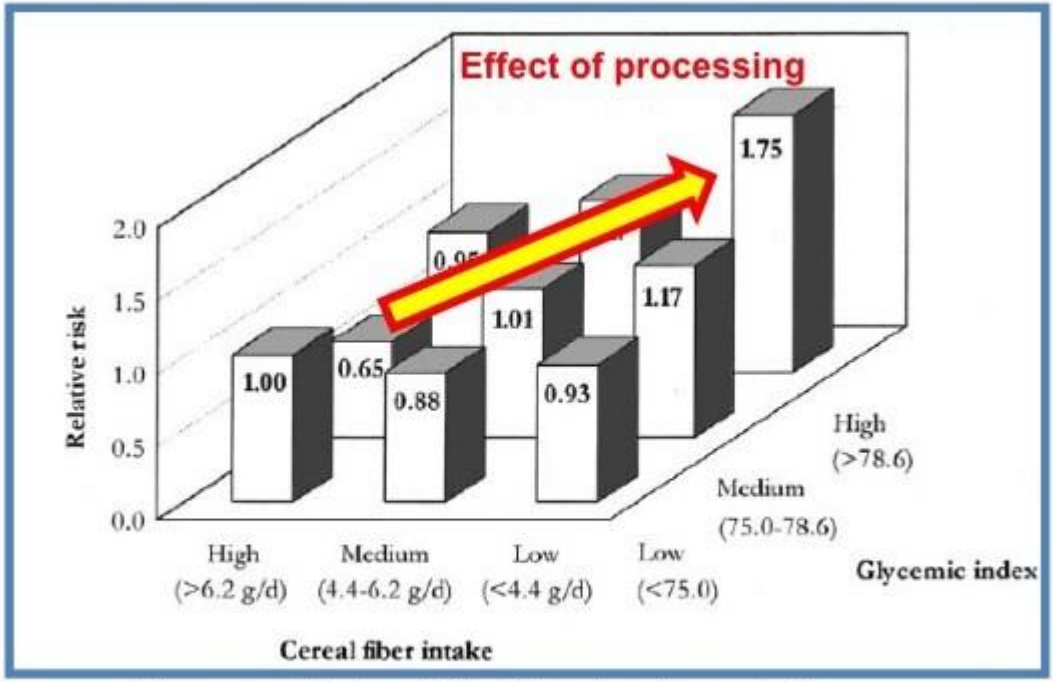
Zhang et al 2012

FTO MUTATIONS AND PROTEIN DIET

- What to do if someone has the genotype for weightloss with Protein diet?
- 25 % protein diet

DIETARY FIBER AND DIABETES RISK

Fiber reduces risk of Diabetes



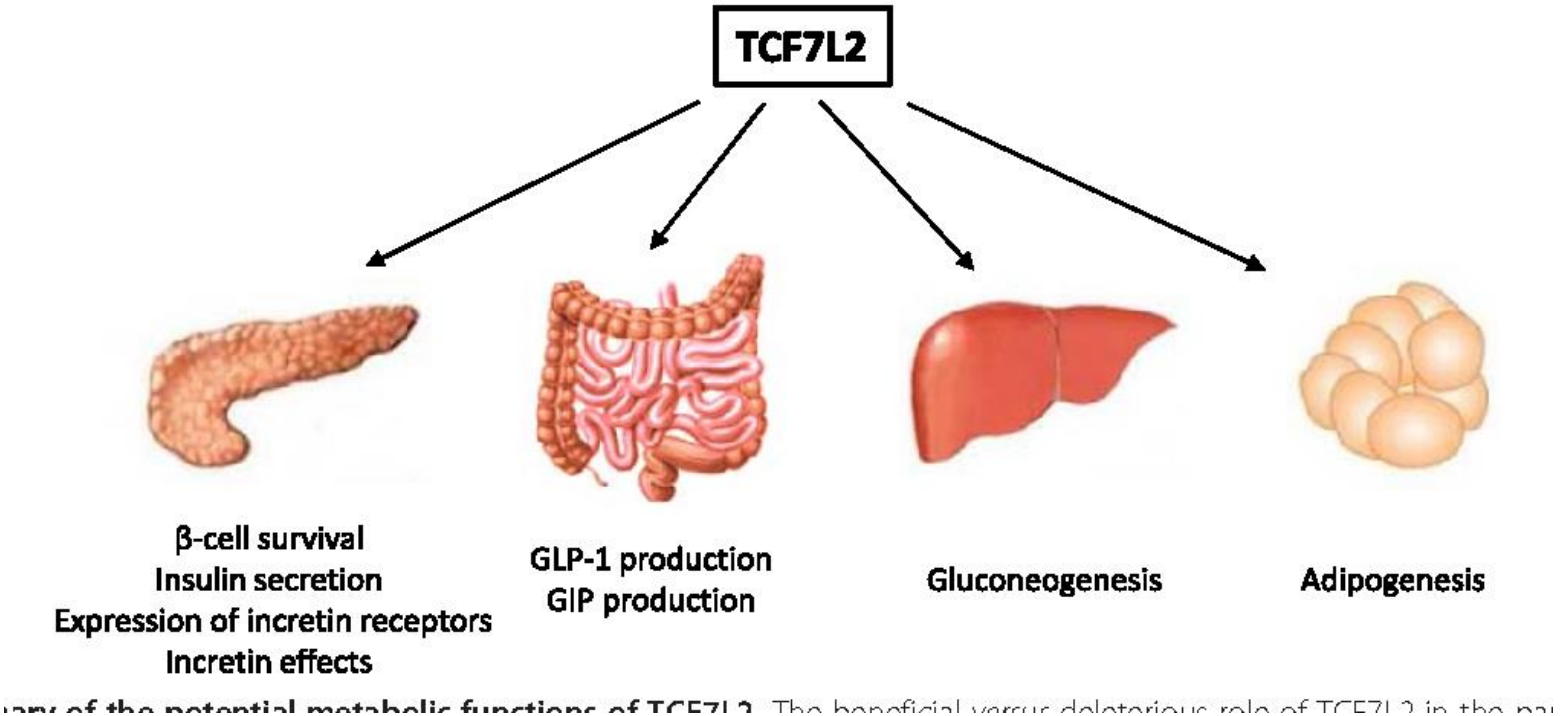
Nurses' Health Study I and II

Am J Clin Nutr. 2004 Aug;80(2):348-56 Walter Willett

NHS I *JAMA*. 1997;277(6):472-477 Willett et al

TCF7L2 AND DIETARY FIBER

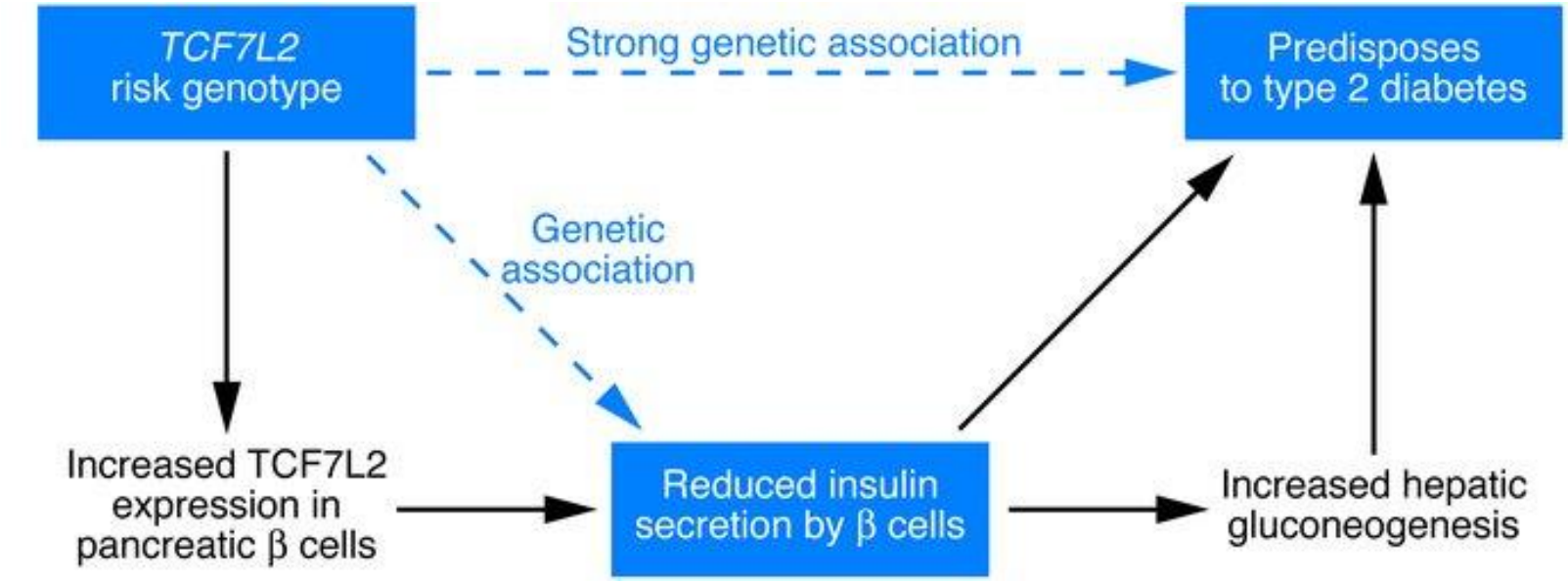
- **TCF7L2 has a multifaceted role in metabolic pathways**



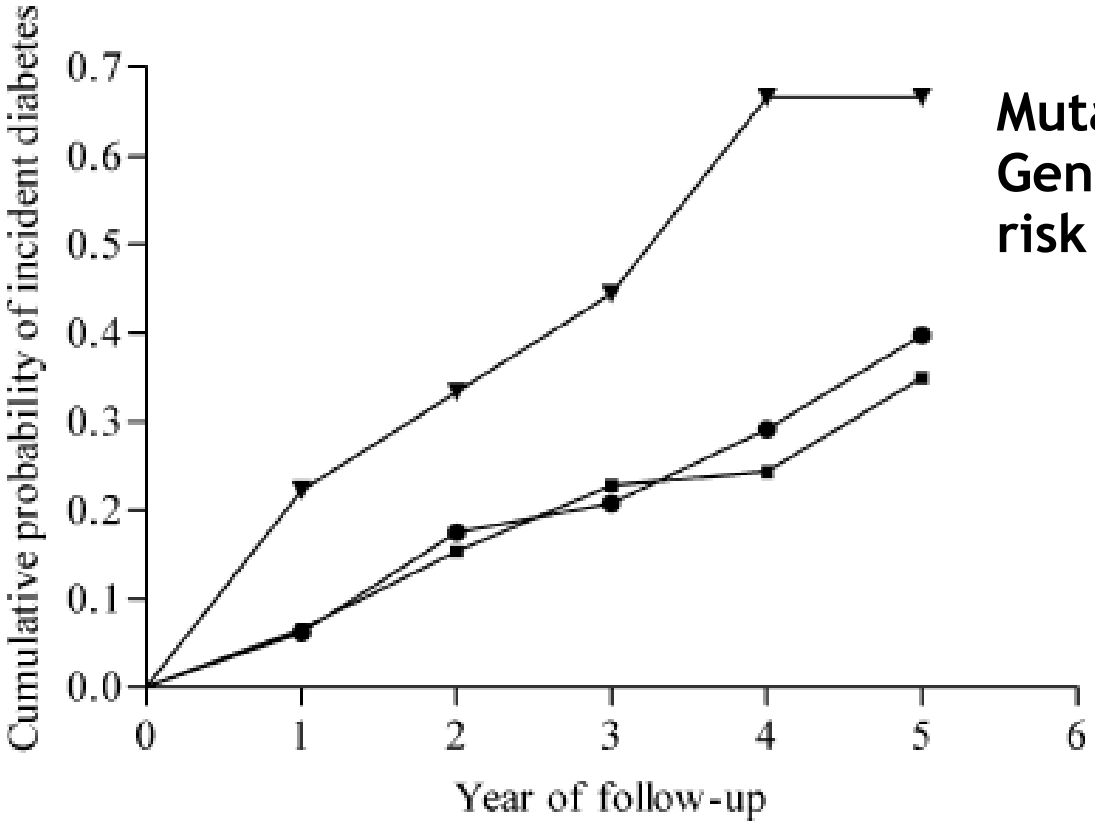
ıary of the potential metabolic functions of TCF7L2. The beneficial versus deleterious role of TCF7L2 in the pa

TCF7L2 AND DIETARY FIBER

- **TCF7L2 is strongly associated with diabetes risk**



TCF7L2 GENOTYPE AND DIABETES RISK

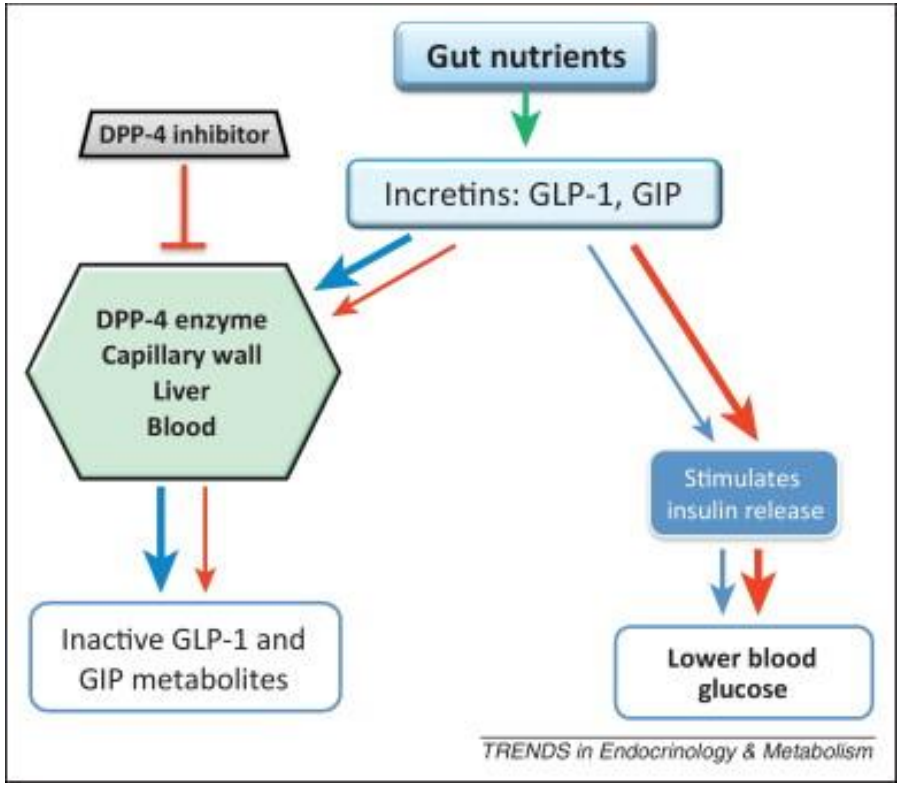


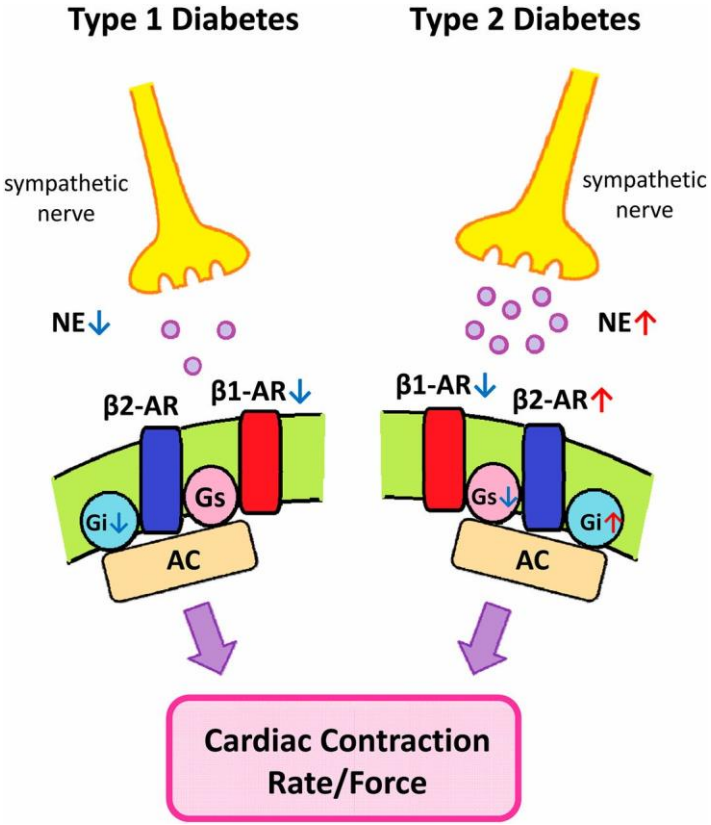
Mutation rs12255372
Genotype: TT at high risk of diabetes

Fig. 1 Cumulative probability of incident diabetes by rs12255372 genotypes in the control group (n=248) during the 4-year follow-up (log-rank test, p=0.009) (Study I). *Inverted triangles*, TT genotype; *circles*, GT genotype; *squares*, GG genotype. Total number of subjects at risk: 248, 244, 225, 194, 136, 62 for years 1–5 post follow-up, respectively

Wang et al 2007

INCRETIN AXIS - DIABETES





TCF7L2 rs12255372 TT GENOTYPE

- Presence of the allele T of the rs12255372 TCF7L2 gene polymorphism is associated with reduced GLP-1-induced insulin secretion.

- Predominant cardiosympathetic activity (higher LF/HF ratio) in response to glucose ingestion in TT subjects was also found. The higher LF/HF ratio found in TT carriers might contribute to explain the association of TCF7L2 gene polymorphism with an increased risk ofT2D.

TCF7L2 GENOTYPE AND FIBER INTAKE - DIABETES

	Hazard ratio (95% CI)[a]	*p* value	Hazard ratio (95% CI)[a]
rs12255372	GT		TT
Overall cohort (*n*=507)			
Unadjusted model	1.20 (0.81–1.78)	0.370	1.80 (0.83–3.91)
Adjusted model[b]	1.17 (0.78–1.74)	0.446	1.71 (0.78–3.73)
Intervention group (*n*=259)			
Unadjusted model	1.21 (0.65–2.25)	0.556	0.54 (0.07–3.96)
Adjusted model	0.89 (0.46–1.70)	0.714	0.61 (0.08–4.52)

Mutation rs12255372
Genotype: TT - reduced diabetes risk with whole grain intake

Wang et al 2007

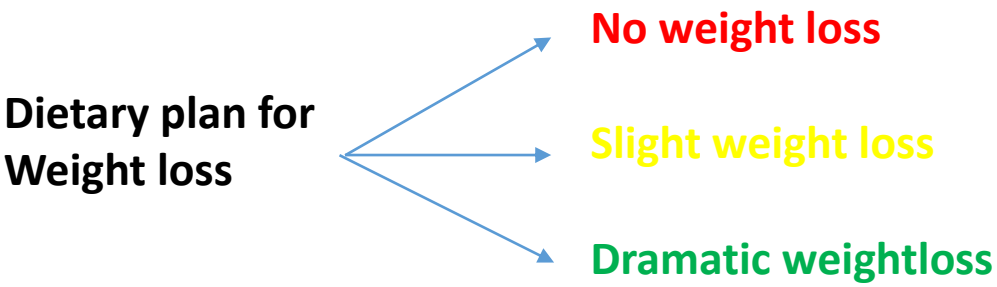
TCF7L2 rs12255372 TT GENOTYPE

- TT carriers respond to increased dietary fiber
- Dietary fiber over 30 gms – 40 gms / day has shown efficacy

WEIGHTLOSS AND GENETICS

Weightloss planning involves dietary changes along with fitness related changes.

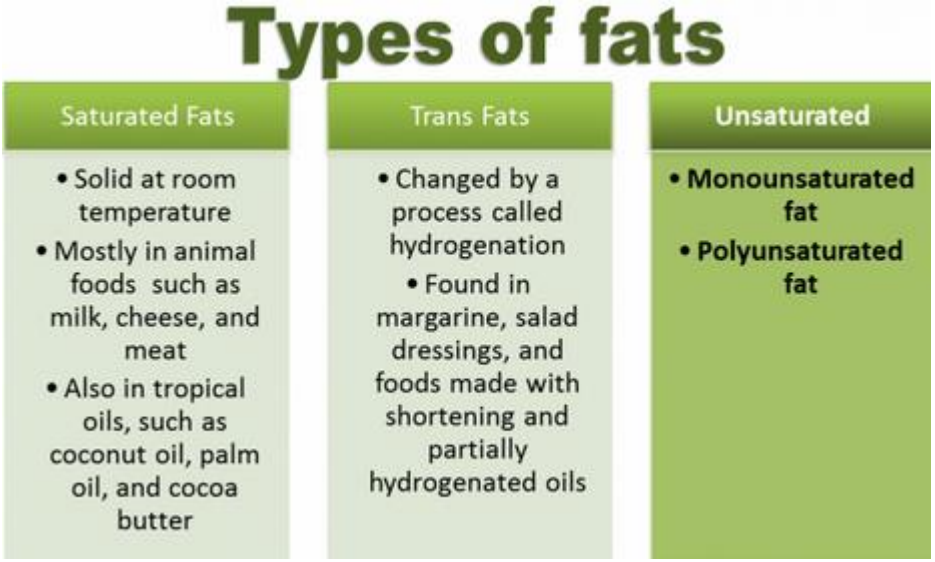
USUALLY 3 OUTCOMES WITH WEIGHTLOSS PLANS:



WHY? ANSWER LIES IN GENETICS

DIET AND WEIGHTLOSS

- Genetics of weightloss with increasing monounsaturated fat consumption
- Genetics of weightloss with increasing unsaturated fat consumption
- Genetics of tasting fat



MONOUNSATURATED FATS

AnantLife

- **Monounsaturated fat is a type of dietary fat. It is one of the healthy fats, along with polyunsaturated fat. Monounsaturated fats are liquid at room temperature, but start to harden when chilled.**

		Monounsaturated Fat (g per 100g - 3,5oz)
1	Olive oil	80.5
2	Almonds, whole	30.9
3	Brazilnuts dried	24.5
4	Butter	21.3
5	Chorizo, Pork And Beef	18.4
6	Beef, Rib, roasted	15.2
7	Duck, Roasted	12.9
8	Herring, Atlantic, Pickled	11.9
9	Pork Sausage, Fresh, Raw	11.8
10	Cream Cheese	9.8
11	Avocado	9.8
12	Cheddar Cheese	9.4
13	Colby Cheese	9.3
14	Pork, Fresh, Ground, Cooked	9.3
15	Goat, Hard Type Cheese	8.2
16	Brie cheese	8.0
17	Olives canned	7.9
18	Gouda Cheese	7.8
19	Blue cheese	7.8
20	Chicken, Wing, Roasted	7.6
21	Parmesan, Hard Cheese	7.6
22	Swiss Cheese	7.3
23	American Cheese	7.2
24	Beef ground, cooked	6.7
25	Mozzarella, Whole Milk Cheese	6.6
26	Pork, Loin, Roasted	6.5
27	Egg, Whole, Fried	6.3
28	Poppy seeds	6.3
29	Cream, Sour, Cultured	6.1
30	Coconut oil	5.8

MONOUNSATURATED FATS AND WEIGHTLOSS

Diet rich in Monounsaturated fats are likely to expedite weight loss. It helps some and does not help others. WHY??

SMART SWAP

ADD AVOCADO

Great news for guac lovers: Eating half an avocado with your lunch can help prevent late-afternoon cravings, says a new study at Loma Linda University in California. Women who did so felt 22 percent more satisfied and had a 24 percent lower desire to nosh three hours later than on days when they'd had an equal-calorie avocado-free lunch. "The fiber, monounsaturated fat and volume of the avocado helped them feel fuller," says study author Michelle Wien, DrPH. A few ways to try:

- ▶ Replace dressing or cheese on your salad with avocado slices.
- ▶ Skip the mayo on your turkey sandwich and sub in mashed avocado.
- ▶ Top chile or soup with avocado hunks instead of cheese and sour cream.

Health

PPARg2 codes for a protein that plays a role in metabolism of fat

ProAla2 allele of PPARg2 shows interaction with diet and weightloss

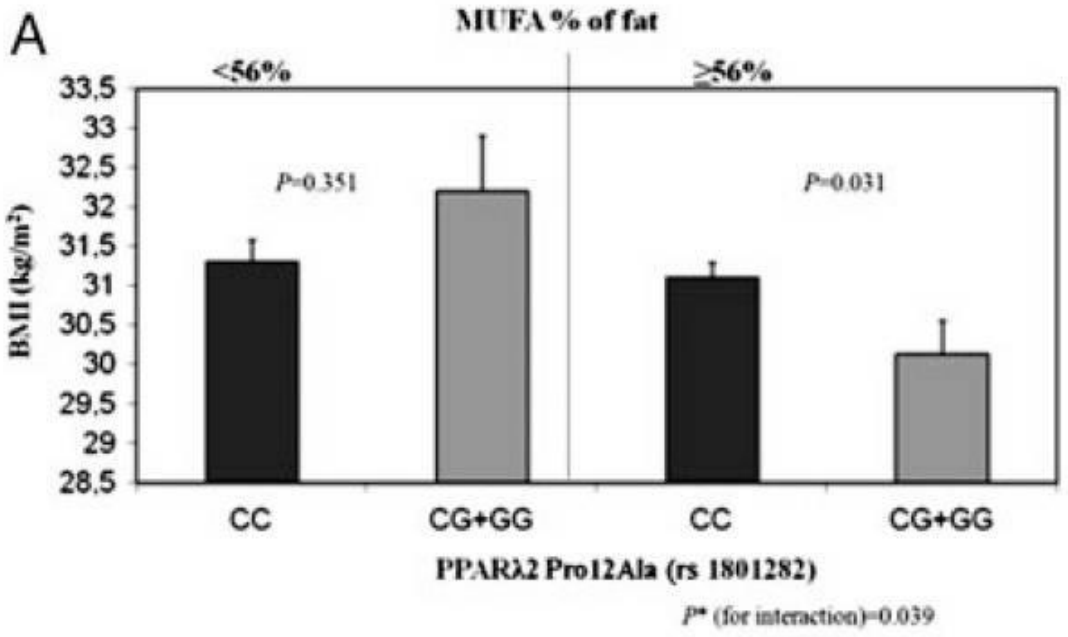
ProAla2 allele of PPARg2 also associated with obesity

PPARG2

- This gene encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors.
- PPARG is a regulator of adipocyte differentiation (fat cells)
- The genes activated by PPARG stimulate lipid uptake and adipogenesis by fat cells
- Deletion of PPARG in mice results in lack of fat accumulation even with a high fat diet

MONOUNSATURATED FATS AND WEIGHTLOSS

Monounsaturated fat rich diet promotes weightloss in individuals with ProAla2 variant of PPARg2

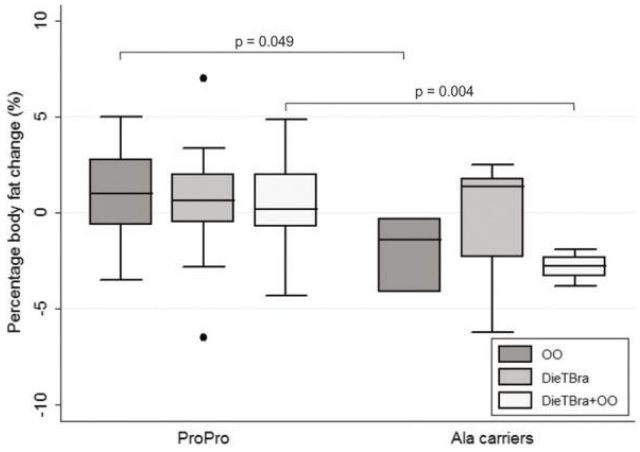


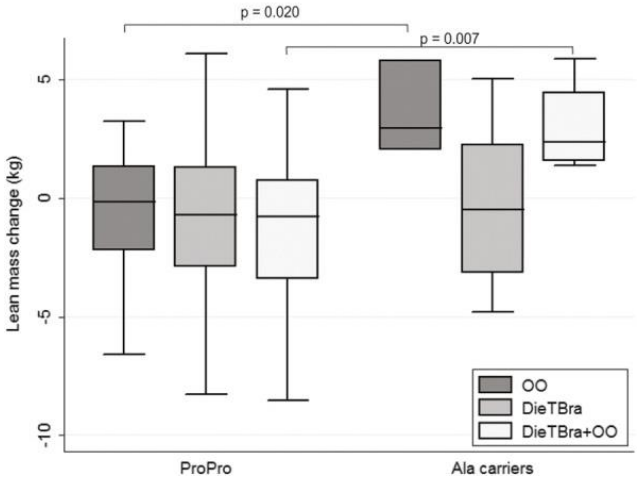
WHAT DOES THIS MEAN?

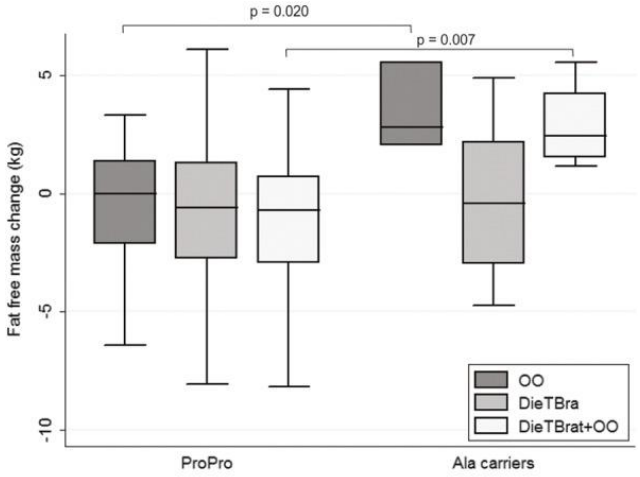
If you have the ProAla2 PPARg2 variant then a diet rich in monounsaturated fats will help expedite weightloss.

OLIVE OIL AND WEIGHTLOSS

Olive oil supplementation promotes weightloss in obese individuals with ProAla2 variant of PPARg2







BMI >35 – Severe Obese

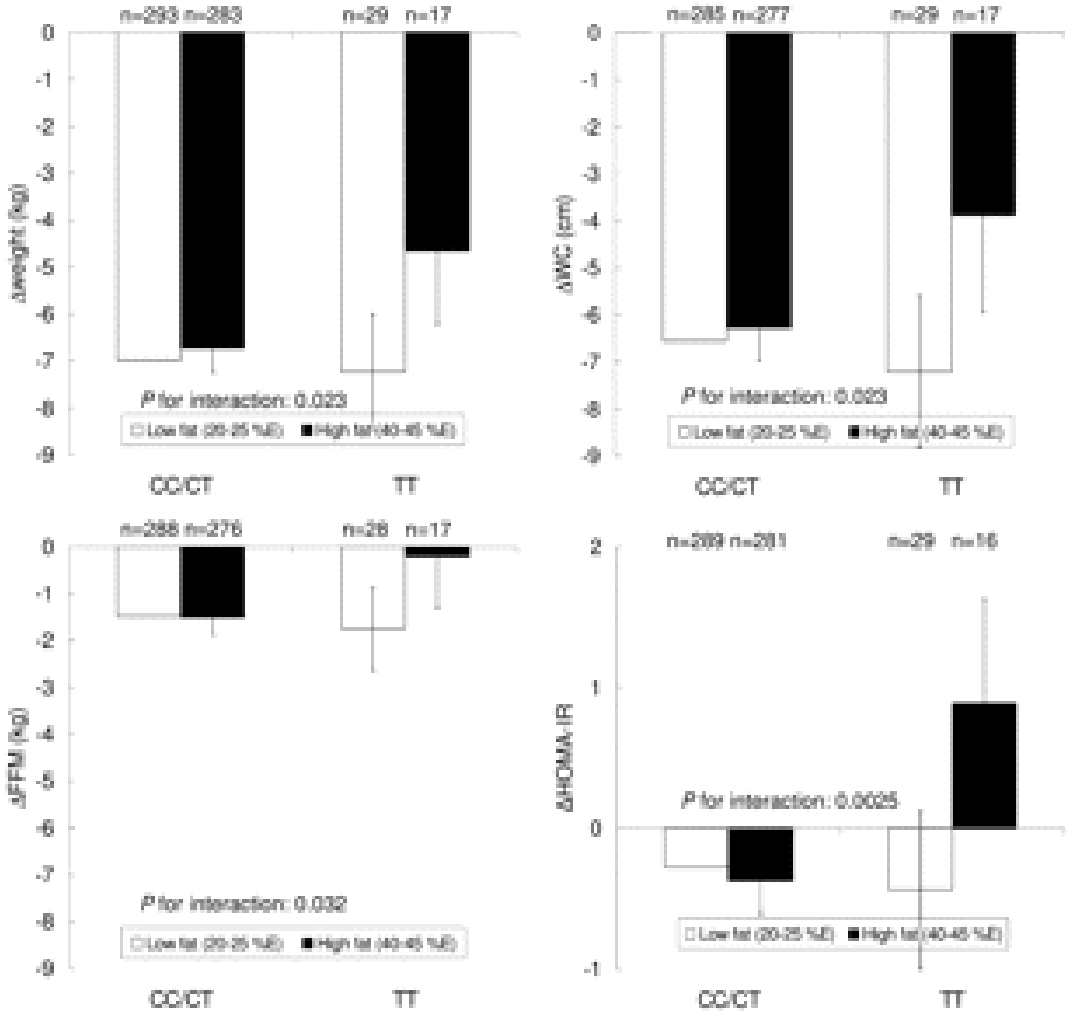
ProAla2 carriers lost fat and gained lean mass with Olive oil supplementation

Rodrigues et al 2018

TCF7L2 AND DIETARY FAT INTAKE

- TCF7L2 regulates GLP-1 release
- GLP-1 induced upon food intake particularly upon intake of fats
- GLP-1 induces fat metabolism
- Certain TCF7L2 variants impact GLP-1 regulation
- The variant results in dysregulation of fatty acid oxidation and impacts energy balance in response to fat intake – ie preferential fat accumulation

TCF7L2 AND REDUCTION IN DIETARY FAT



TT genotype associated with:
- Increased weight gain, waist circumference, insulin resistance with Fat intake

Decreased parameters with Reducing Dietary Fat intake

Grau et al 2018

TCF7L2 AND SATURATED FAT INTAKE

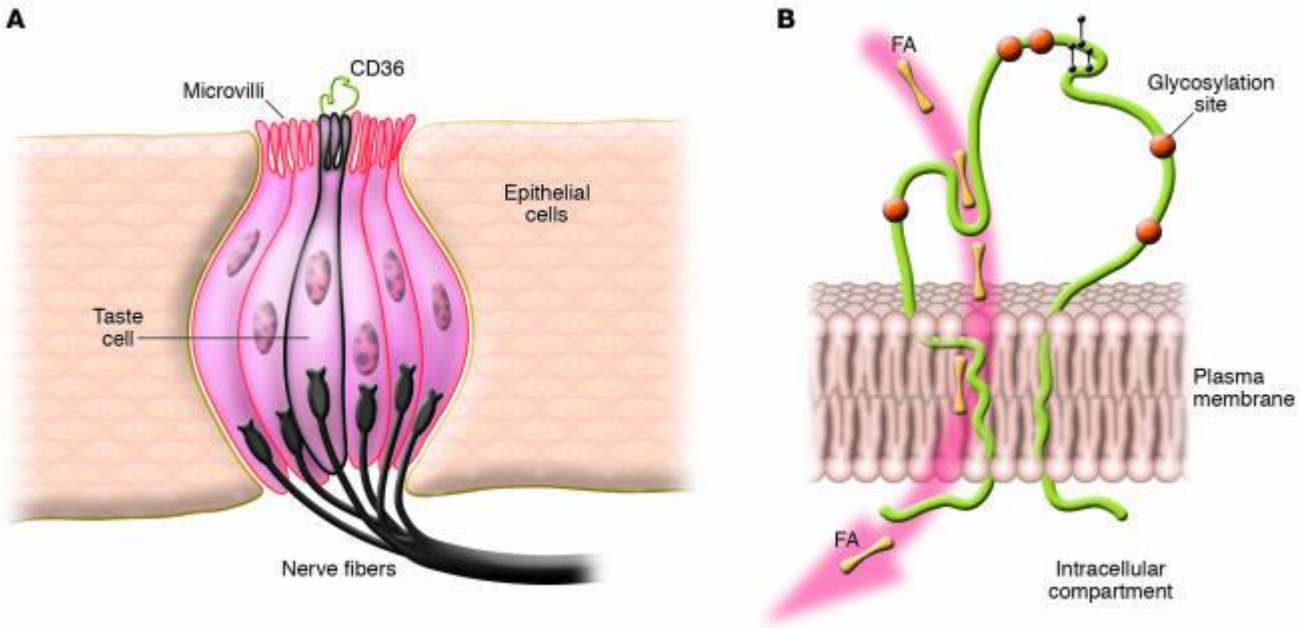
- TCF7L2 variants regulate risk of metabolic syndrome
- Metabolic syndrome is a group of health problems that include too much fat around the waist, elevated blood pressure, high triglycerides, elevated blood sugar, and low HDL cholesterol. Together, this group of health problems increases your risk of heart attack, stroke, and diabetes.
- Higher Saturated Fat Intake increases risk of metabolic syndrome in TT carriers of TCF7L2 – via GLP-1 TCF7L2 axis

WHAT TO DO IF SOMEONE IS CARRYING TT VARIANT ON TCF7L2?

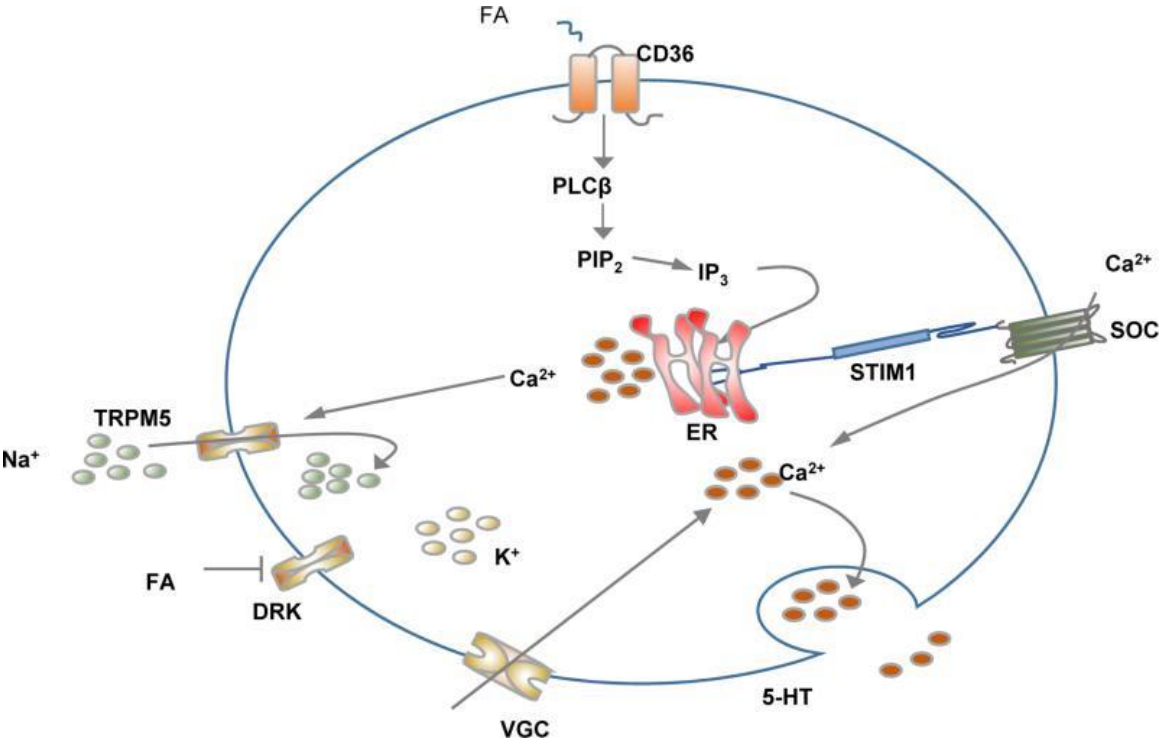
- Intake of fats and saturated fats associated with metabolic disorders
- Very responsive to reduction in dietary fat intake
- Need to be prescribed a low fat diet
  - Increase intake of vegetables and fruits
  - Moderate intake of meat and poultry – lean cuts
  - Moderate intake of dairy products – low fat

CD36 AND ABILITY TO TASTE FAT

- **CD36, the protein identified as a taste receptor for fat, is an integral membrane glycoprotein and a member of a family of proteins expressed both at the cell surface and within lysosomes.**

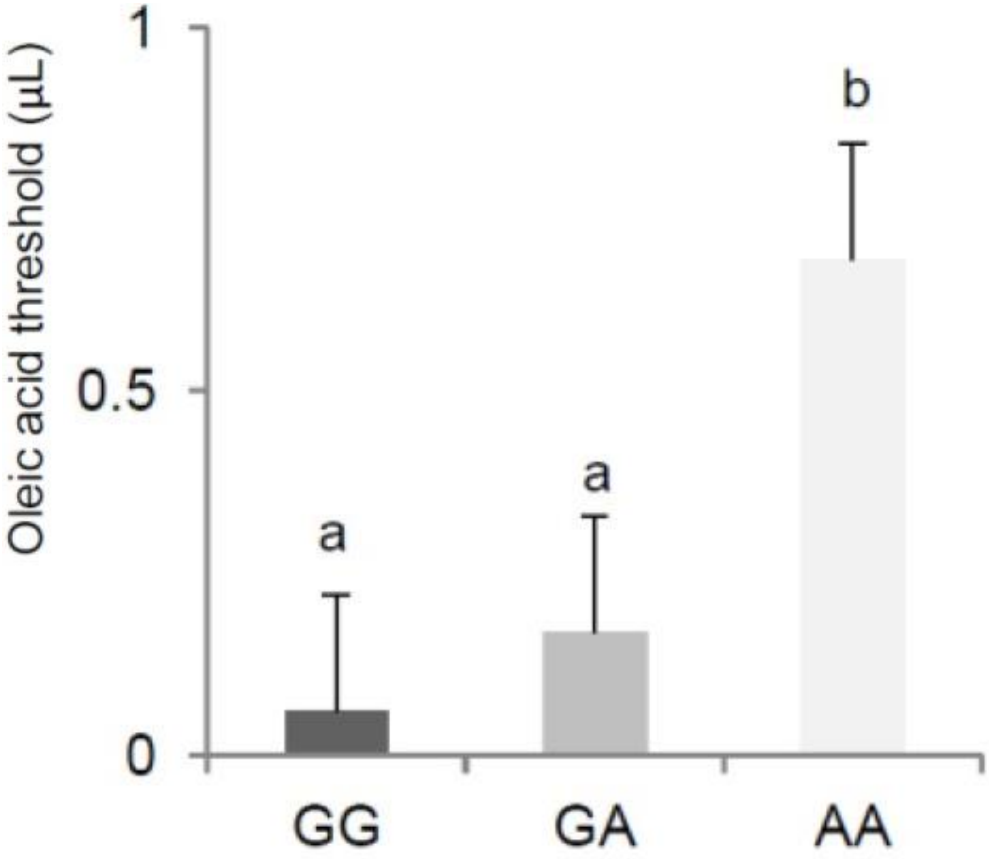


CD36 AND ABILITY TO TASTE FAT



Fatty acids bind to CD36, resulting in activation of enzymatic pathways which promotes calcium release - this also results in calcium intake via SOC channels, together this promotes release of neurotransmitter - serotonin.

CD36 VARIATION AND ABILITY TO TASTE FAT



Variation in CD36 has been associated with a heightened / reduced ability to taste fat

G allele likely reduces the threshold needed for activation of neurotransmitters

Melis et al 2015

WHAT TO DO IF SOMEONE IS CARRYING G ALLELE OF CD36?

- G allele carriers - Can taste fat at low amounts
- A allele carriers - Need higher fat content to taste

- G allele carriers - fat content can be reduced in their diet without a compromise of taste

- A allele carriers - reduction in fact content compromises taste

DNA BASED WEIGHTLOSS PLANS WORK

Dietary & Fitness planning for weightloss needs to incorporate DNA based planning for maximum efficacy

Non – DNA based plan for Weight loss

- No weight loss
- Slight weight loss
- Dramatic weightloss

DNA based plan for Weight loss

- ~~No weight loss~~
- ~~Slight weight loss~~
- Dramatic weightloss