Strategies for Applying Epigenetics in Your Practice

Proven Protocols for Clinical Success

Dr. Robert G. Silverman

DC, DACBN, MS, CNS, CCN, CSCS, CIISN, CKTP, CES, DCBCN, HKC, FAKTR

www.DrRobertSilverman.com







"Your genetics load the gun. Your lifestyle pulls the trigger."

author unknown

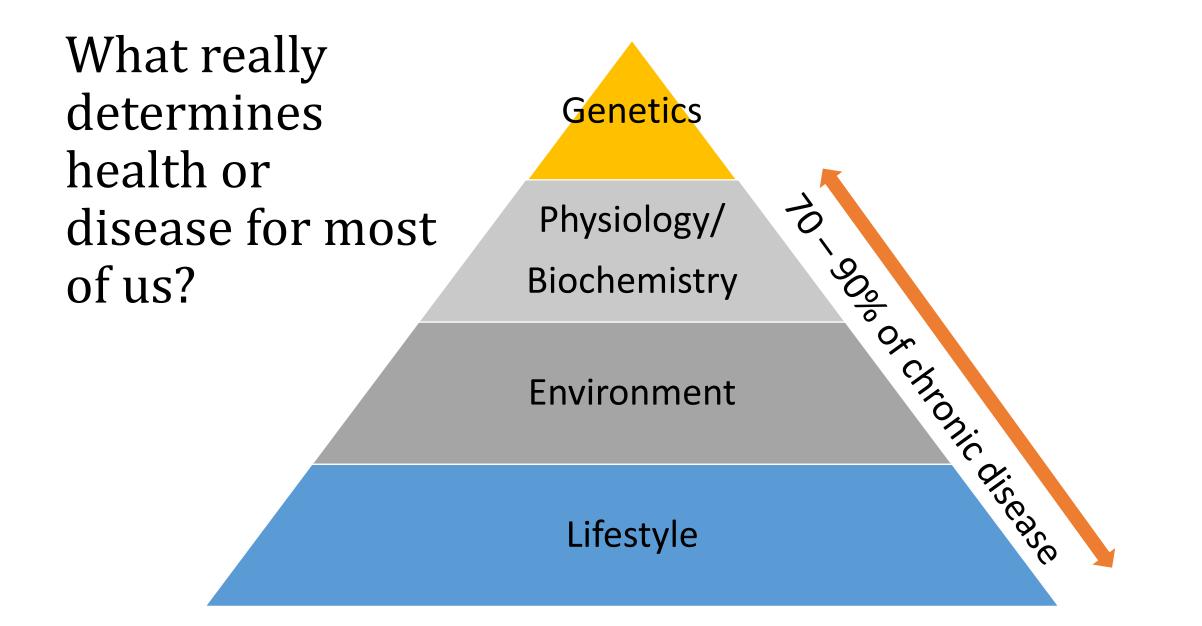
Your DNA is not your destiny

• This means that genes may load the gun, but **environmental factors** pull the trigger



Translation:

Genes are your **potential** but require a certain environment in order to be expressed



Genetics Overview

- Genomics: high level view of genes, their functions and interrelationships between other genes
- Genetics: looks at mechanism of action at the gene level
- Includes:
 - 1. Chromosomes
 - 2. DNA
 - 3. Genes
 - 4. Polymorphisms (frequency > 1% of the population)

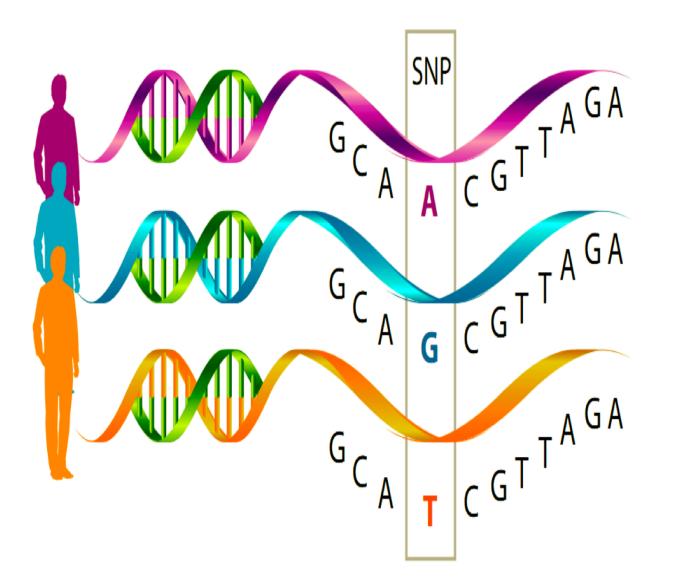
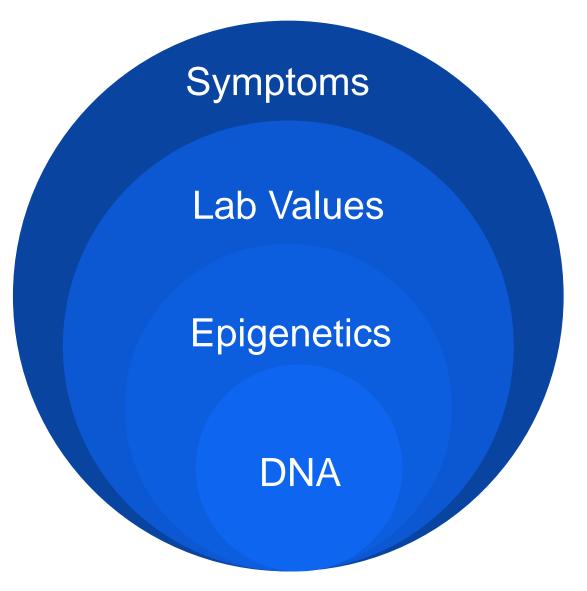
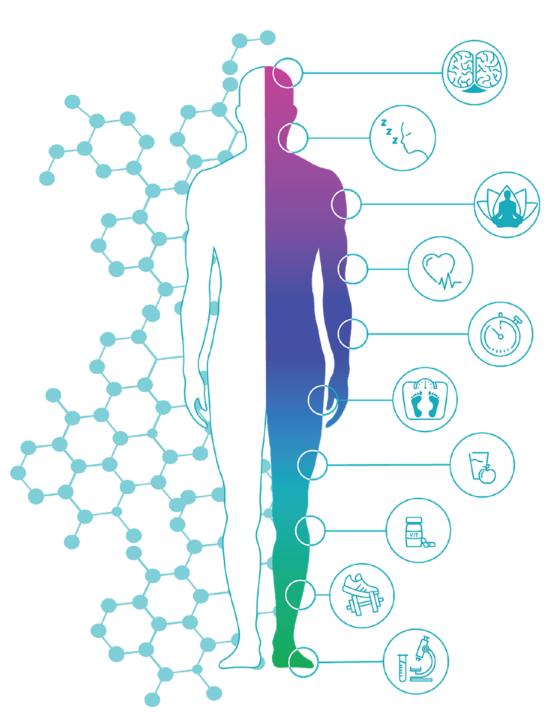
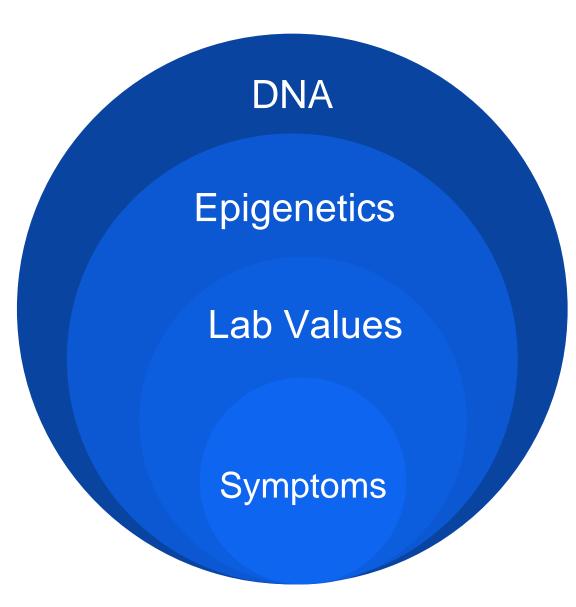


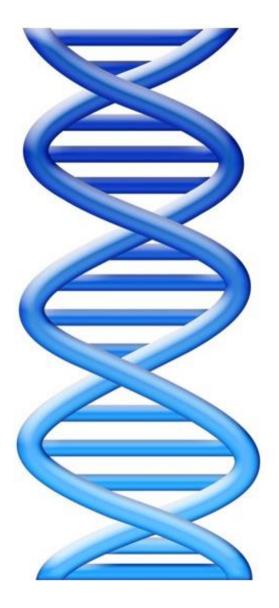
Image source: https://blogs.kcl.ac.uk/editlab/files/2018/07/prs1.jpg





But is there a way to know before the symptoms start?



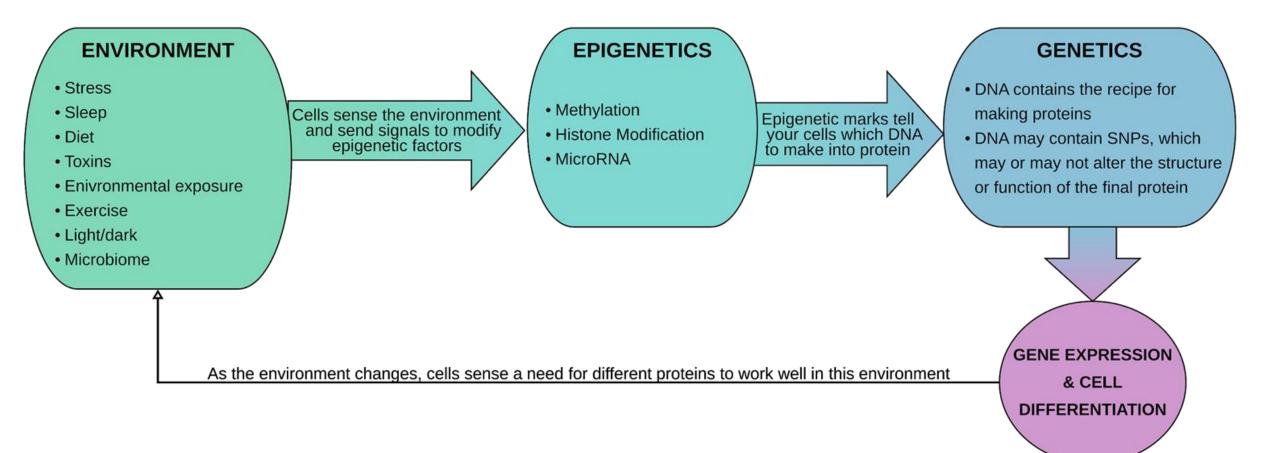


DNA

"The Blueprint of Life"



Epigenetics Summary



How Does This Happen?



https://mediad.publicbroadcasting.net/p/wuwm/files/styles/medium/public/201401/epig

Twin Astronauts



Twin Studies



Twin A

Sedentary Smokes Poor diet Hypertension Hyperglycemia Risk for CVD

Twin B

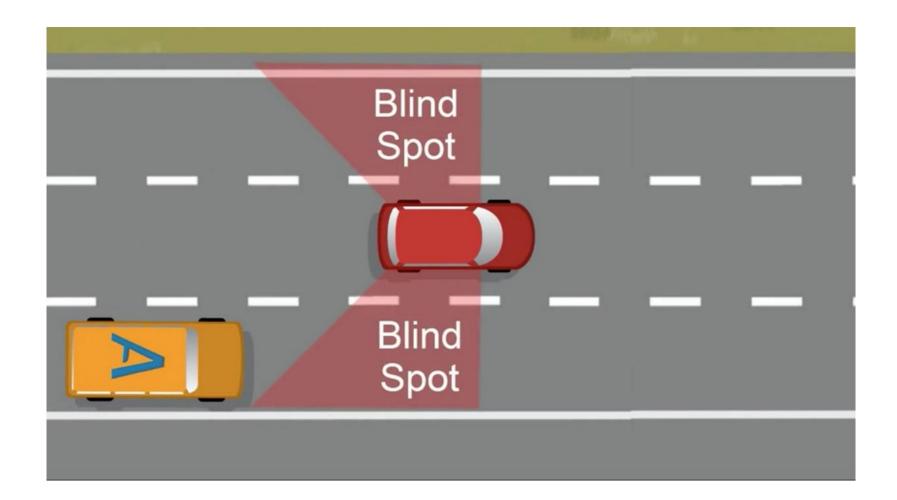
Exercises Healthy diet Low stress Finished a 5K Clean bill of health

Same Environment, Different Outcomes





Power Of Genetics



Examples of Epigenetic Effects

- Stress
- Diet
- Sleep
- Toxins
- Environmental exposure
- Exercise
- Light/dark
- Microbiome

MTHFR



https://www.sott.net/image/s13/279814/full/folate vs folic acid 1.jpg

Possible Effects Of MTHFR

MTHFR Gene Mutation May Increase the Risk of:

Learning Disorders Mood Disorders Fibromyalgia Neurodegeneration Heart Disease Digestive Problems Addictive Behaviors Down Syndrome Autolmmunity Chronic Fatigue



Folate

People with similar genetic markers may be predisposed to folate deficiencies.

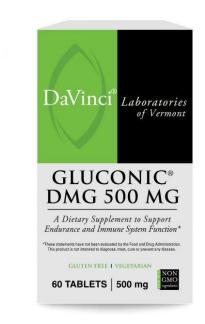
Gene	SNP	Variant	Impact
FOLH1	rs61886492	+/+	High
MTHFR	rs1801131	+/-	- Medium
MTHFR	rs1801133	+/-	- Medium

MTHFR

Stress B Capsules	1 cap with meal
Active Folate B12 Chewable	1 daily
Gluconic DMG 500 mg	1 BID







How These Traits Affect You

This page provides a high-level snapshot of the clinical significance of each trait within this panel. The results are in two categories: traits that are ranked high, medium or low impact as well as traits for which there is an explicit result (i.e. categorical such as "yes" or "no"). At the end of this page are a summary of any non-reportable (NR) traits. The results for these traits are unable to be determined from the sample submitted. Recommendations are made for traits with high or medium impact only.



Impact Traits	Impact	Learn More
1 Injury Risk - Disc Degeneration	≡нісн	Page 11
2 Vitamin C		Page 12
3 Vitamin D3		Page 13
4 Injury Risk - Muscle Damage	LOW	
5 Magnesium	LOW	
6 Musculoskeletal Pain	LOW	

Categorical Traits	Result	Learn More
1 Muscle Fiber Type	Slow Twitch	Page 14

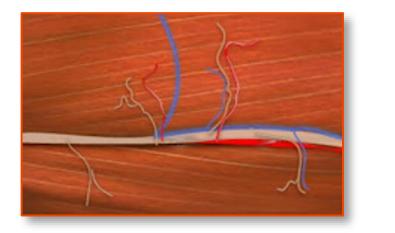
Dr. Rob Musculoskeletal Panel

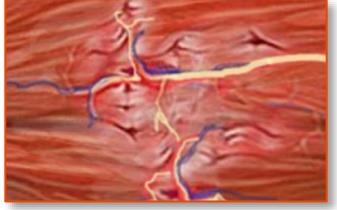
Health Action Plan

Epigenetic Influences

- Exercise
- Exercise type
- Recovery
- Nutrition
- Pain

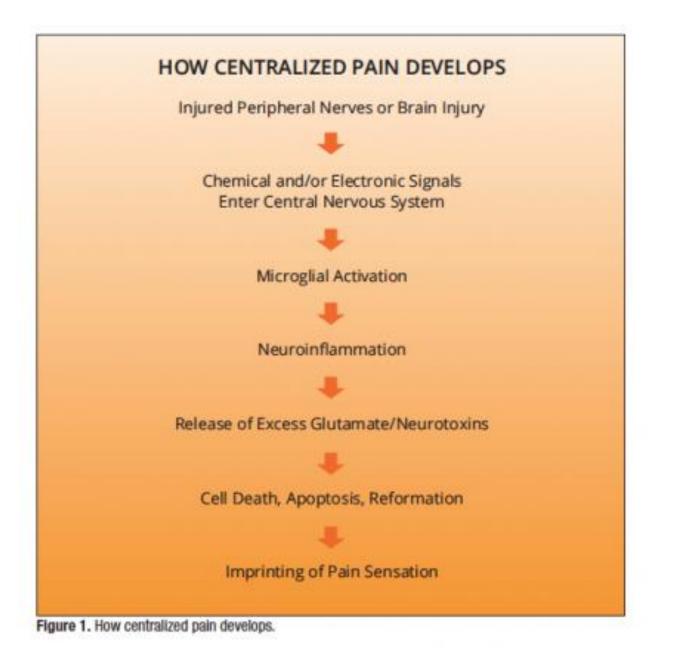
HEALING IS A PROCESS





PRE-INJURY Healthy Tissue **INJURED** Strained Tissue **HEALED** Scar Tissue

Scar tissue left on the muscle after healing restricts the muscle fibers, nerves and vessels causing pain and leaving the muscle less flexible



https://www.practicalpainmanagement.com/resources/clinical-practice-guidelines/clinical-diagnosis-centralized-pain-age-icd-10

Musculoskeletal panel

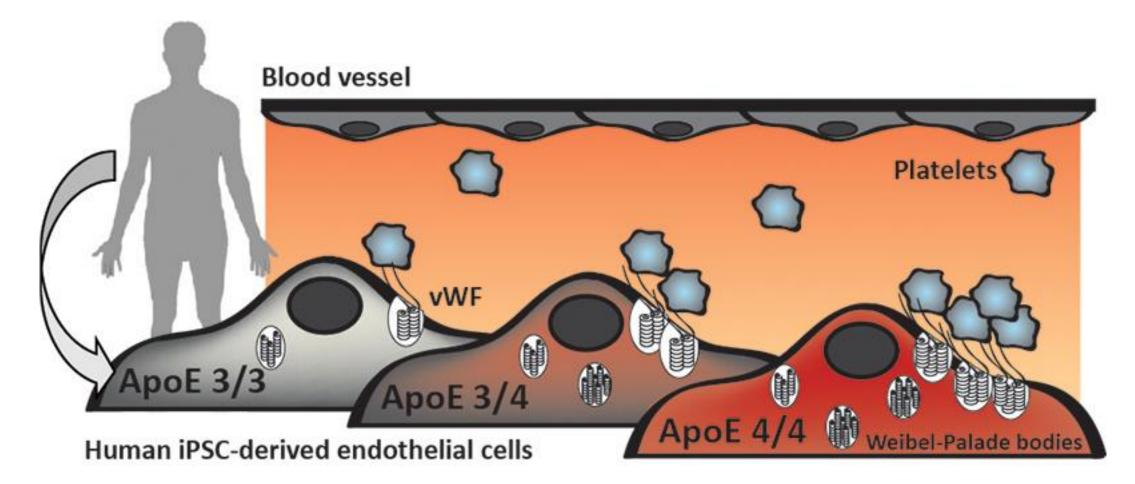
Cx-2 Solution	3 caps daily
Enz-Flame	1 scp daily
Phytocann-Omega	1 sg daily







APOE







Alzheimer's Disease

People with similar genetic markers may be at a higher risk for developing Alzheimer's disease.

Gene	SNP	Variant	Impact
APOE	rs7412	E3/E3	- Medium
SORL1	rs11218343	+/+	High
APOE	rs429358	E3/E4	High
BIN1	rs744373	+/-	Medium
RAB20	rs56378310	+/-	Medium

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In	npact Traits	Impact	Learn More
1	Inflammation	НІСН	Page 11
2	Oxidative Stress	≡ніgн	Page 13
3	Concussion with TBI	- MEDIUM	Page 14
4	Mild Cognitive Impairment	- MEDIUM	Page 15
5	Omega 3	LOW	

Dr. Rob TBI/ Concussion Panel

Health Action Plan

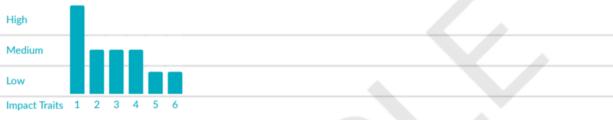
Epigenetic Influences

- Omega 3 levels
- Omega 3 intake
- Nutrition
- Smoking
- Alcohol
- Exercise

How These Traits Affect You

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In	npact Traits	Impact	Learn More
1	Inflammation	НІСН	Page 11
2	Celiac Disease		Page 13
3	Concussion with TBI	- MEDIUM	Page 15
4	Irritable Bowel Syndrome (IBS)		Page 16
5	Gluten Sensitivity	LOW	
6	Lactose Intolerance	LOW	

Health Action Plan

Epigenetic Influences

- Head Trauma
- Food Allergies
- Food Sensitivities
- Microbiome
- Leaky Gut
- Antibiotics

APO E status

- "Apolipoprotein E plays a critical part in the maintenance, repair and growth of neurons, and seems to have an important part in the neural response to brain injury"
- "The E4 isoform results in reduced growth and branching of neurites in vitro and seems to have an important part to play in the neural response to injury"

Smith C, Graham DI, Murray LS, et al. Association of APOE e4 and cerebrovascular pathology in traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2006;77:363–6. Ariza M, Pueyo R, del Mar Matar in M, et al. Influence of APOE polymorphism on cognitive and behavioral outcome in moderate

and severe traumatic brain injury. J Neurol Neurosurg Psychiatry 2006;77:363-6.

АроЕ

- ApoE gene on chromosome 19
- Encodes the instructions for making protein that helps transport cholesterol and other types of fat in the bloodstream
- 3 main focus:
 - ApoE2 relatively rare. If you inherit this allele it's protective of developing Alzheimer's
 - ApoE3 most common allele, no real effect
 - ApoE4 25 to 30 percent of population. Most common Alzheimer's allele

APOE4

Finding:

- Support concept that there is reduced response to anti-dyslipidemia treatment in E4 carriers
- Reinforces usefulness of APOE genotyping in predicting patientresponse to lipid lowering therapies

Alzheimer gene linked to higher risk of severe COVID-19

- Having 2 copies of e4 variant of ApoE gene linked to double risk of severe COVID-19
- Study is latest to suggest genetics may play a role in why some people are more vulnerable to coronavirus than others
- ApoE4 gives rise to proteins involved in carrying facts around the body
- Known to affect cholesterol levels and process in inflammation

Alzheimer gene linked to higher risk of severe COVID-19 (cont'd)

- Researchers found:
- 383,000 European ancestry. 9022 positive for two copies of e4 variant – increased risk of dementia 14 times
- Positive COVID-19: March 16 to April 26
 - 37 people positive with two E4 two times risk of severe COVID-19

Conclusion: Possible that the role of ApoE in the immune system is important in the disease

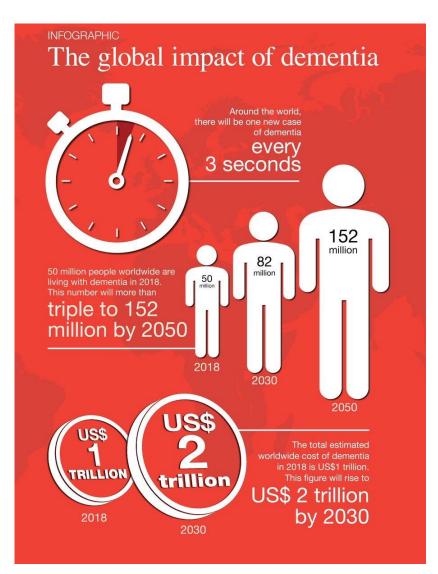


Concussion linked to brain changes in people at genetic risk for Alzheimer's

Brain. Jan. 11, 2017

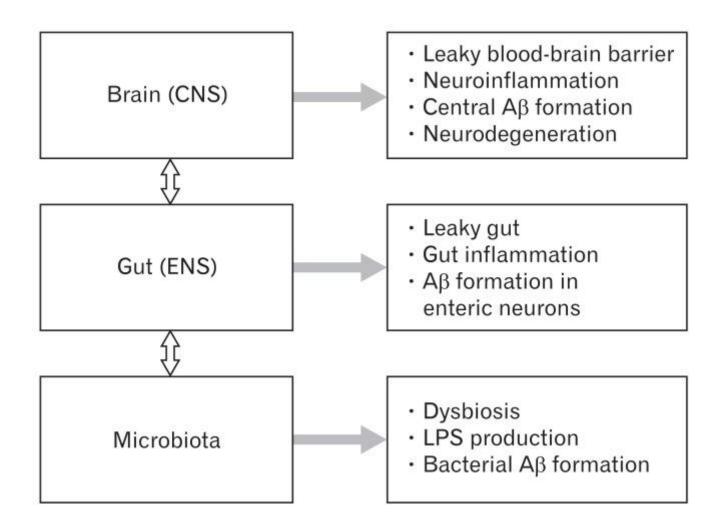
ALZHEIMER'S DISEASE

- 6th leading cause of death in the US; 7th in the world
- 2000-2015: heart attack deaths decreased 11%; Alzheimer's deaths increased 123%
- 1 in 3 seniors die from Alzheimer's/dementia kills more than breast and prostate cancer combined
- 2018 Alzheimer's/dementia (US) cost \$277 billion
- By 2050 Alzheimer's/dementia (US) could cost > \$1.1 trillion
- Someone in the US develops the disease every 65 seconds



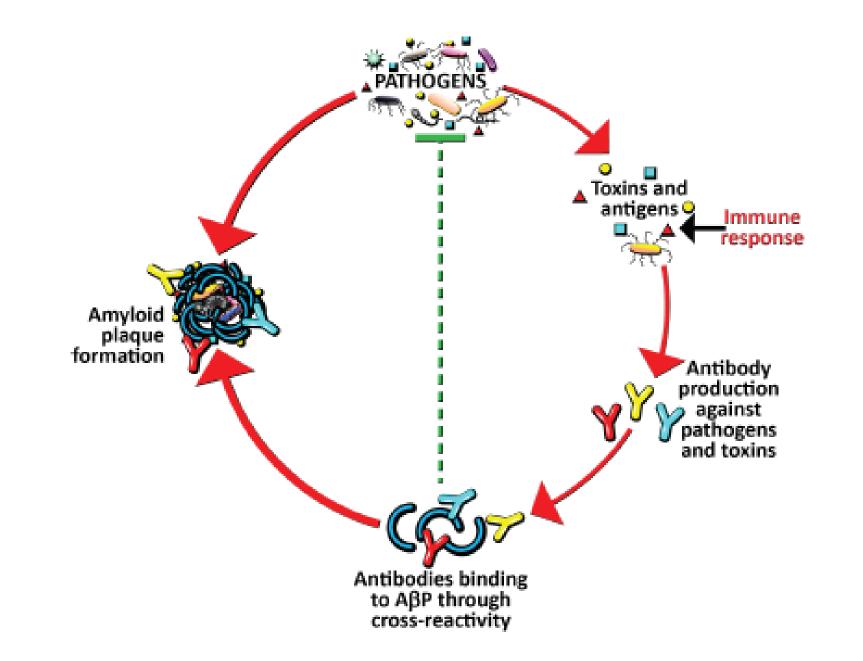
Credit: World Alzheimer's Report 2018

Disturbances of the brain-gut-microbiota axis in Alzheimer's disease



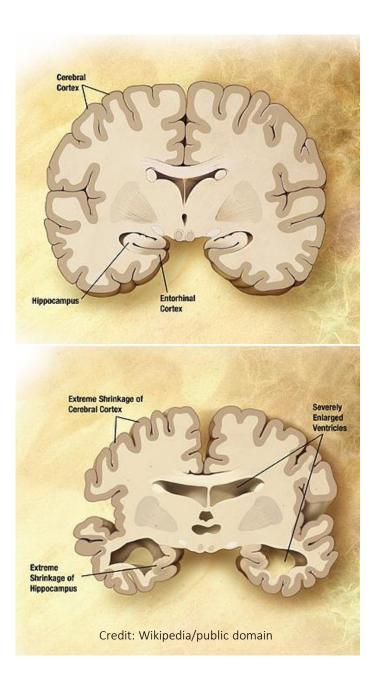
Kowalski K, Mulak A. Brain-Gut-Microbiota Axis in Alzheimer's Disease. J Neurogastroenterol Motil. 2019;25(1):48–60. doi:10.5056/jnm18087

Detox for cognitive decline

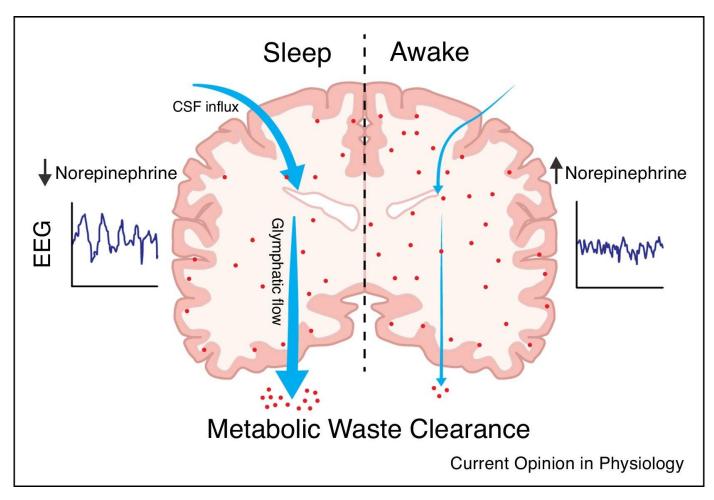


Sleep and Alzheimer's

Study found – when young, healthy men were deprived of just one night of sleep, they had higher levels of tau protein in their blood

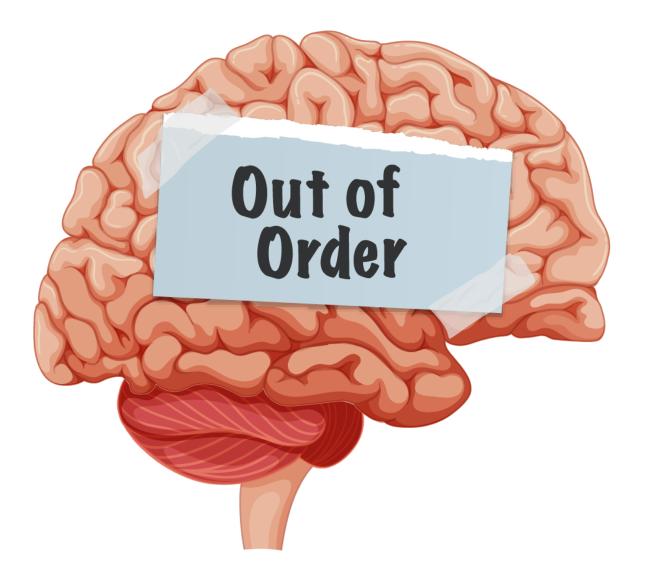


Relationship between glymphatic system function and brain states



Head injuries may lead to early Alzheimer's

- Contact sports that can result in concussions football lead to early onset Alzheimer's
- Conclusions drew by looking at post-mortem Alzheimer's cases
- Alzheimer's onset could be "accelerated" by up to 9 years



5 measures that lower Alzheimer risk

- 5 behaviors associated with lower risk for Alzheimer's disease:
 - 1) Exercise
 - 2) Not smoking
 - 3) Moderate drinking
 - 4) Mediterranean diet
 - 5) Mentally stimulating activities
- The more you follow them, the lower the risk

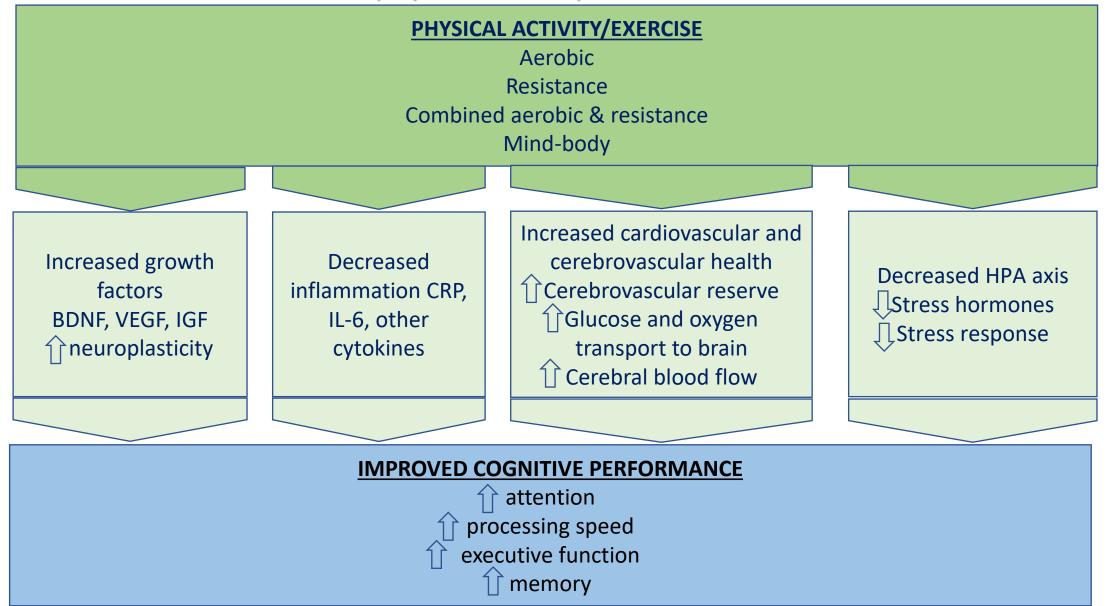
Klodian D, Denis AE, Kumar BR, et al. Healthy lifestyle and the risk of Alzheimer dementia. Findings from 2 longitudinal studies. *Neurology*, 28 Jul 2020;95(4):e374-e383

5 measures that lower Alzheimer risk (cont'd)

2 databases used:

- 1845 patients average age 23
- 920 patients average age 81
- All free of Alzheimer's at the start
- Followed for average of 6 years
- 608 developed Alzheimer's disease
- Those with 2 or 3 healthy lifestyle factors 37% reduced risk
- Those with 4 or 5 healthy lifestyle factors 60% reduced risk

Overview of potential biological mechanisms underlying cognitive gains with physical activity and exercise



Adria Q, Marilyn ML, Gail E. Journal of Aging Research, 14 May 2020. https://doi.org/10.1155/2020/1407896

Sleep/Alzheimer's disease

When young healthy men were deprived of 1 night of sleep – had higher levels of tau (biomarker for Alzheimer's disease) in their blood than when they had full night of rest



Christian B, Kaj B, Henrik Z, et al. Effects of acute sleep loss on diurnal plasma dynamics of CNS health biomarkers in young men, Neurology Jan 2020. Online

Omega-3 needed to provide brain benefits

- 33 participants Alzheimer's risk factors
- 15 participants APOE4 gene
- Treatment group took 2 grams DHA
- Control group took placebo
- Researchers gathered samples of:
 - Blood plasma
 - $\circ \, \text{Cerebrospinal fluid}$
- Tested for EPA and DHA

IC Arellanes, N Choe, V Soloman, et al. Brain delivery of supplemental docosahexaenoic acid (DHA): A randomized placebo-controlled clinical trial, *EBioMedicine*, 2020, doi.org/10.1016/j.ebiom.2020.102883

Omega-3 needed to provide brain benefits (cont'd)

- After 6 months:
 - Patients who took omega-3 200% more DHA in blood
 - 28% more in cerebrospinal fluid

Takeaway: Blood plasma levels may not indicate how much is reaching the brain

Conclusion: E4 carriers, despite having same dose, has less omega-3s in brain

IC Arellanes, N Choe, V Soloman, et al. Brain delivery of supplemental docosahexaenoic acid (DHA): A randomized placebo-controlled clinical trial, *EBioMedicine*, 2020, doi.org/10.1016/j.ebiom.2020.102883

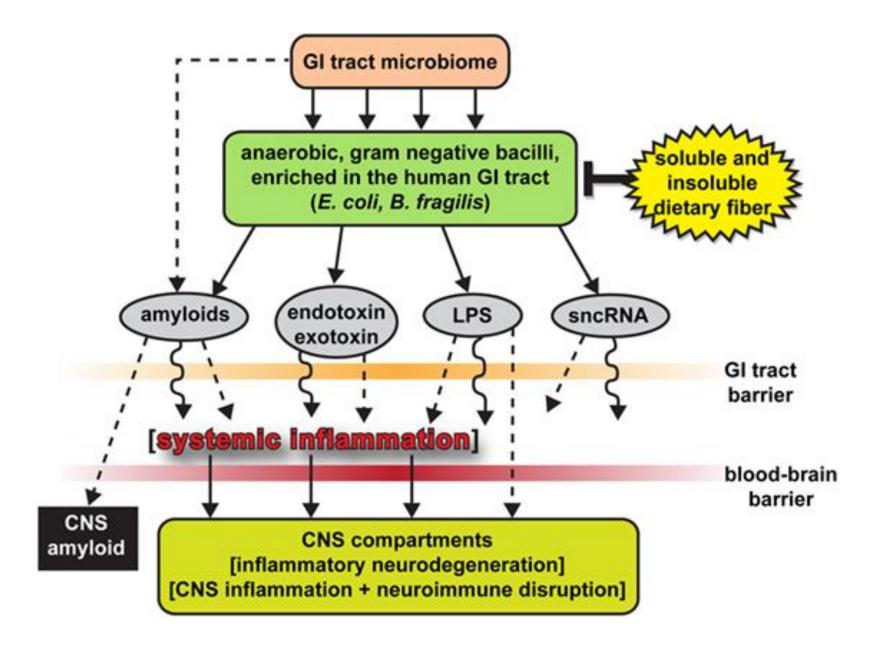
Body weight has impact on brain function

- 35,000 spect from 17,000 patients
- Low cerebral blood is a large predicator of Alzheimer's disease

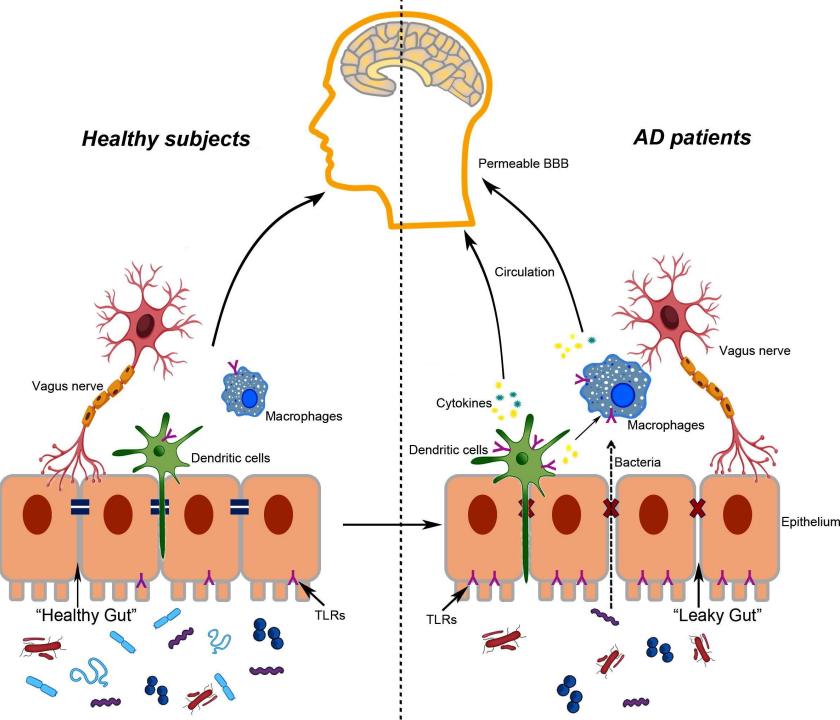
Conclusion:

"Study shows being overweight or obese seriously impacts brain activity and increased risk for Alzheimer's disease as well as many psychiatric and cognitive conditions". – Dr. Daniel G. Amen

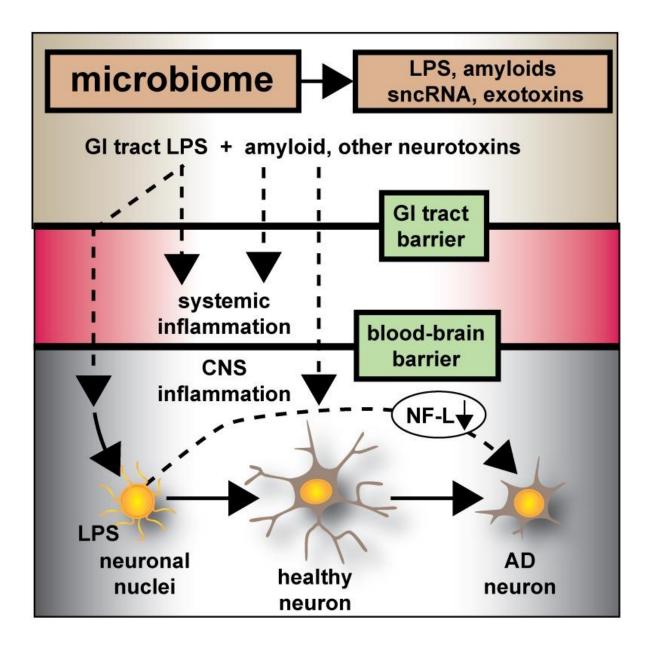
Daniel GA, Joseph W, Noble G, Andrew N. **Patterns of Regional Cerebral Blood Flow as a Function of Obesity in Adults**. *Journal of Alzheimer's Disease*, 2020; 1 DOI: <u>10.3233/JAD-200655</u>



Potential implications of TLRs and gutbrain-axis for AD

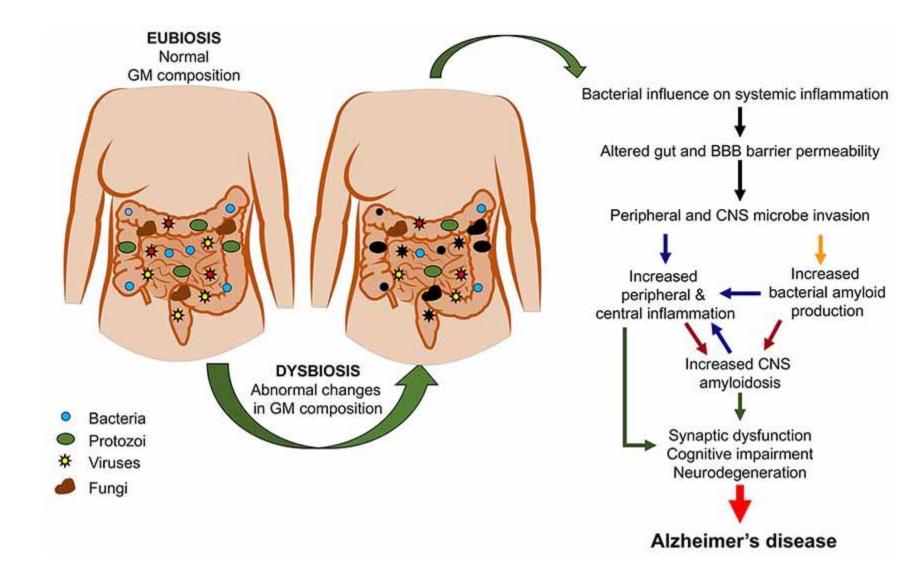


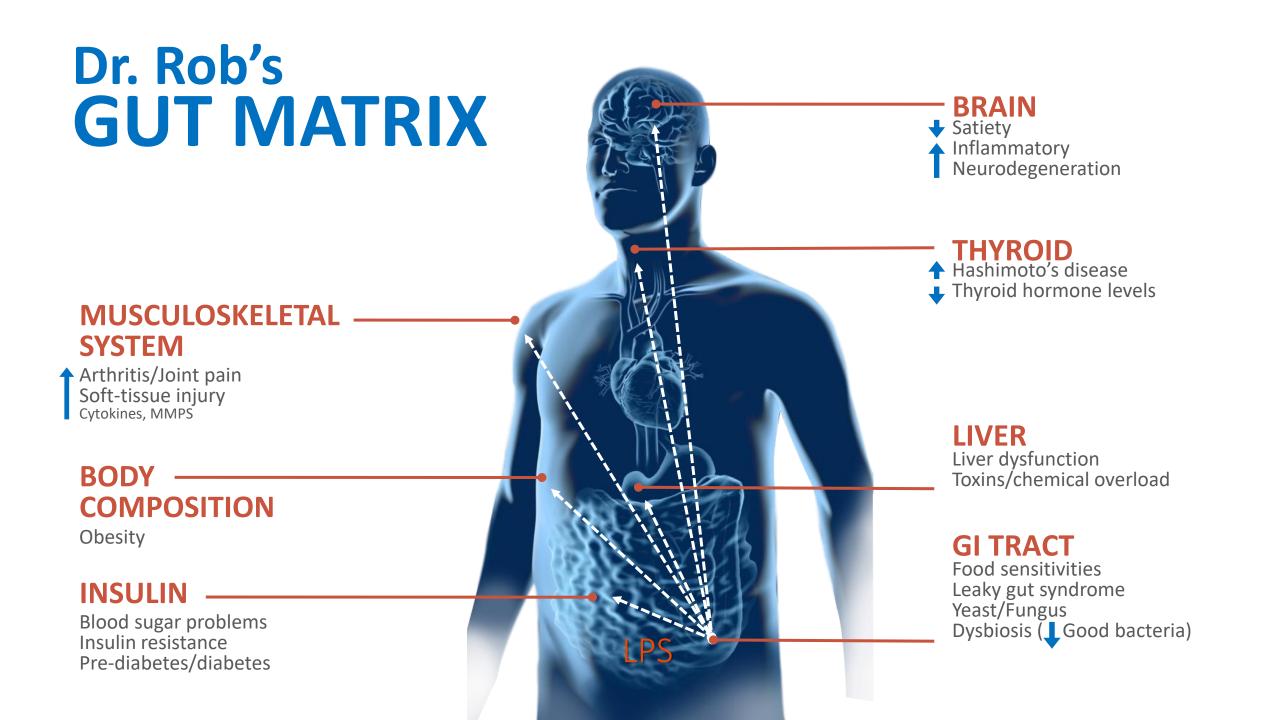
Caixiu L, Shuai Z, Yueli Z, et al. *Computational and Structural Biotechnology Journal*. 2019;17:1309-17



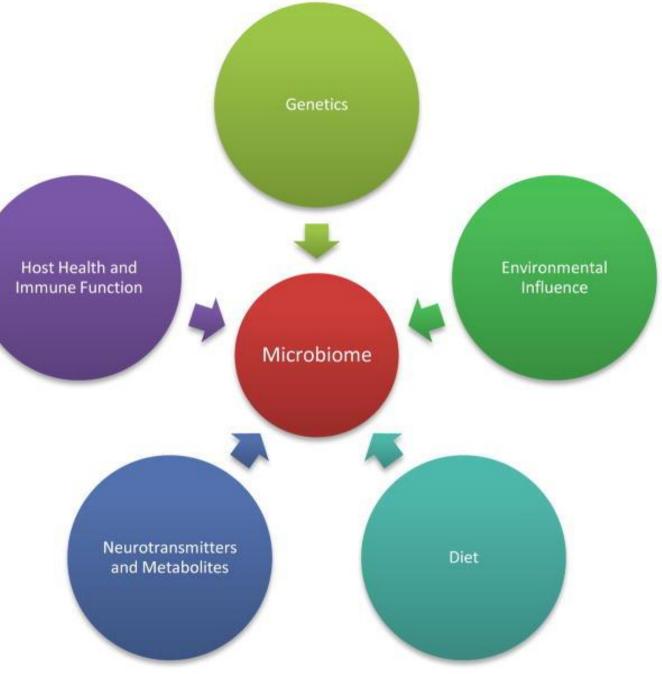
Lukiw WJ, Cong L, Jaber V, Zhao Y. Microbiome-Derived Lipopolysaccharide (LPS) Selectively Inhibits Neurofilament Light Chain (NF-L) Gene Expression in Human Neuronal-Glial (HNG) Cells in Primary Culture. *Frontiers in Neuroscience*. 2018 ;12:896

From gut dysbiosis to Alzheimer's disease (AD)





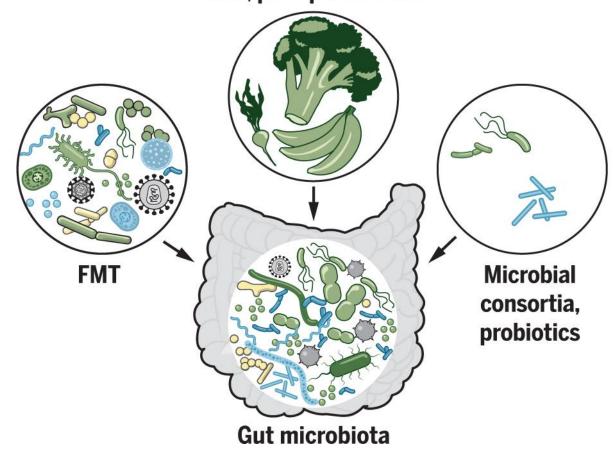
Factors affecting gut microbiota composition



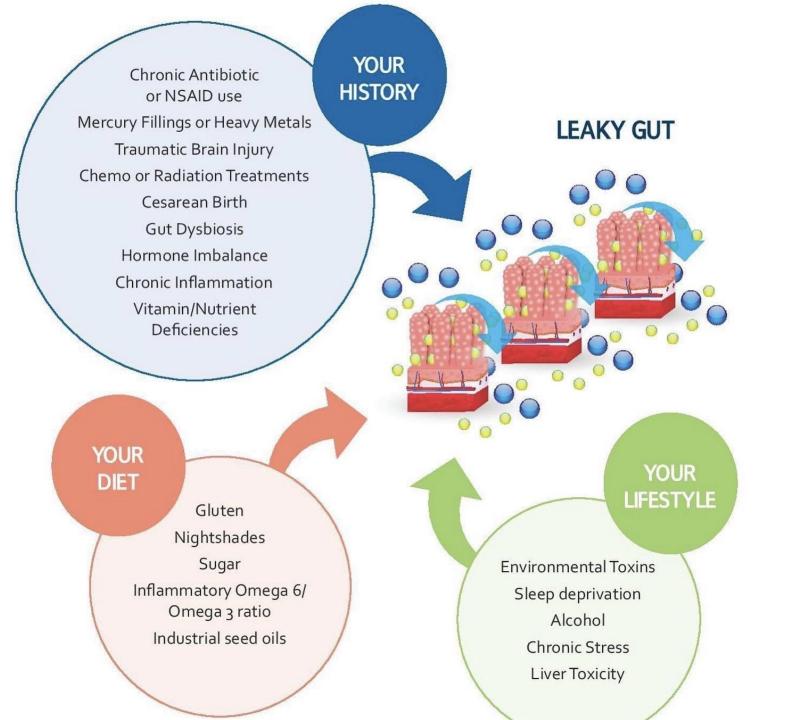
Ghaisas S, Maher J, Kanthasamy A. Gut microbiome in health and disease: Linking the microbiome-gut-brain axis and environmental factors in the pathogenesis of systemic and neurodegenerative diseases. *Pharmacol Ther*. 2016;158:52-62

Strategies to alter gut microbiota

Fecal microbiota transplant (FMT) involves transfer of fecal microbiota from a donor to another individual. Alternatively, microbial consortia (targeted formulations used to augment host microbiota) are being developed. Diet, prebiotics, and postbiotics can also influence the microbial community.



Diet, pre-/postbiotics



Leaky gut triggers

Solvingleakygut.com

Common food additive impacts gut bacteria

E 621

TRANS FAT

E 320

SODIUM NITRATE

Results: Demonstrates a novel paradigm of deconstructing hostmicrobiota interactions that indicate the microbiota can be directly impacted by these commonly used food additives (emulsifiers), in a manner that drives intestinal inflammation

Gut. 2017 Aug;66(8):1414-1427

POTASSIUN BROMATE

0

Gut bacteria influences depression

- Analyzed fecal microbiome data
- 1054 people with diagnosis of depression
- The Flemish Gut Flora Project
- Coprococcus and Dialister absent from the guts of people with a diagnosis of depression



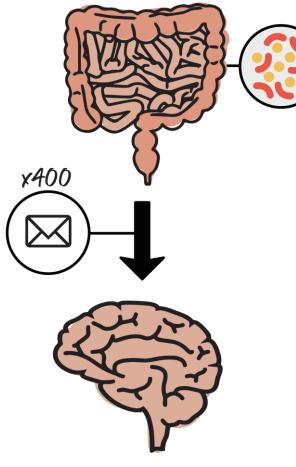


GUT-BRAIN CONNECTION

Getting to the root of the broken brain

Zhu X, Han Y, Du J, et al. OncoTarget. 2017 May 10;8(32):53829-53838

GUT TO BRAIN

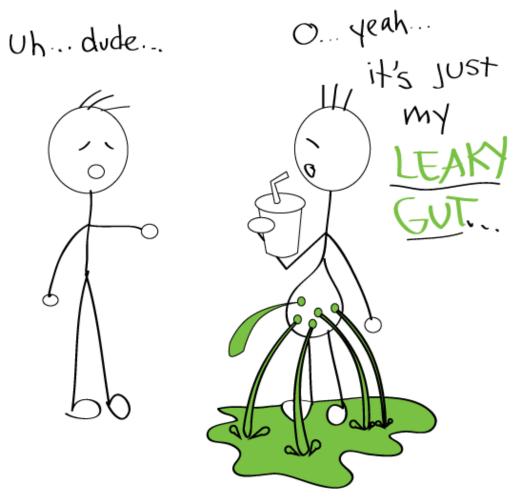


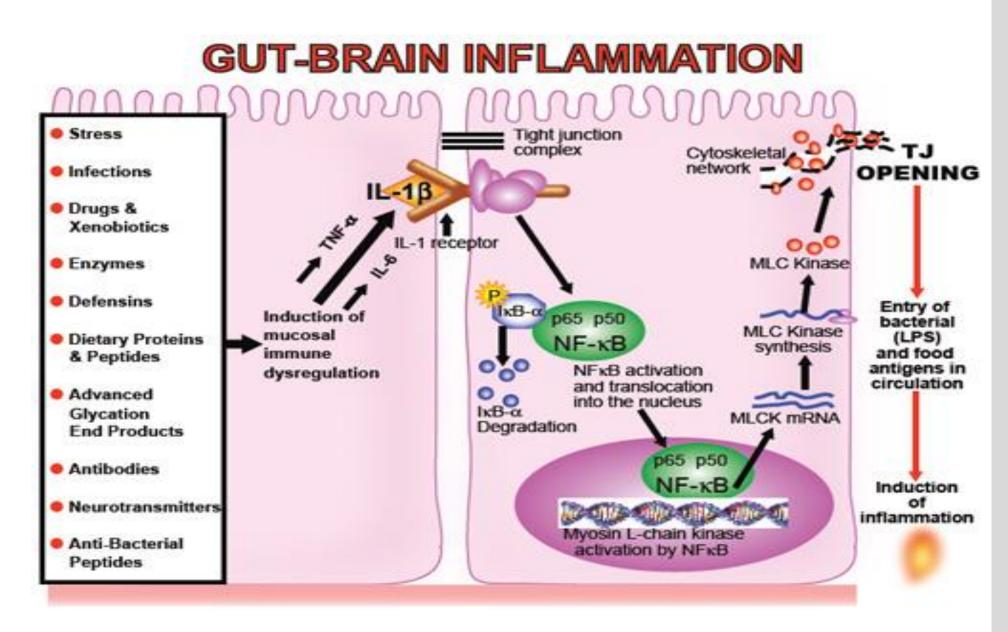
- 400 times the amount of messages from gut to brain than the brain to the rest of the body
- Over 1,000 species
- 3 lbs. of bacteria in your gut
- Trillions of bacteria in the gut
- 20 million bacteria genes; 2,000 genes in humans
- More bacteria than cells in our body
- Gut contains more neurotransmitters than brain

GUT TO BRAIN cont'd

• Gut:

- Produces vitamins
- Digests food
- Regulates hormones
- Excretes toxins
- Produces healing compounds
- To treat the brain must remove cause of inflammation such as leaky gut





"A high percentage of abnormal [Intesinal Permeability (leaky gut)] IPT values were found among patients with autism (36.7%) and their relatives (21.2%) compared with normal subjects (4.8%)."

Exercise influence on the microbiome gutbrain axis

 Aerobic exercise improves diversity and abundance of genera from Firmcutes phylum – may be the link between the positive effects of exercise on the gut and brain

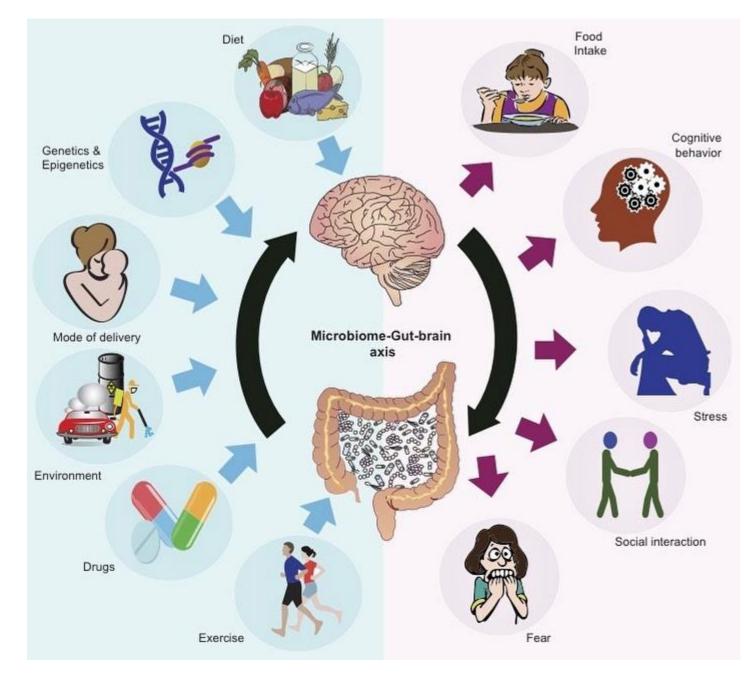


Summary of effects of altered microbiota on the gut-brain axis contributing to obesity

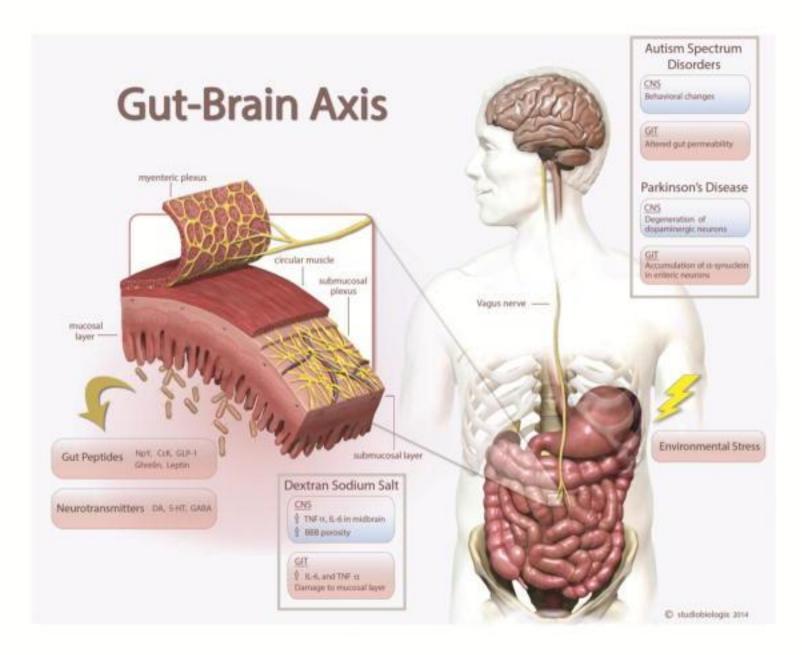


The Gut-Brain Axis, the Human Gut Microbiota and Their Integration in the Development of Obesity. Front. Physiol., 12 July 2018

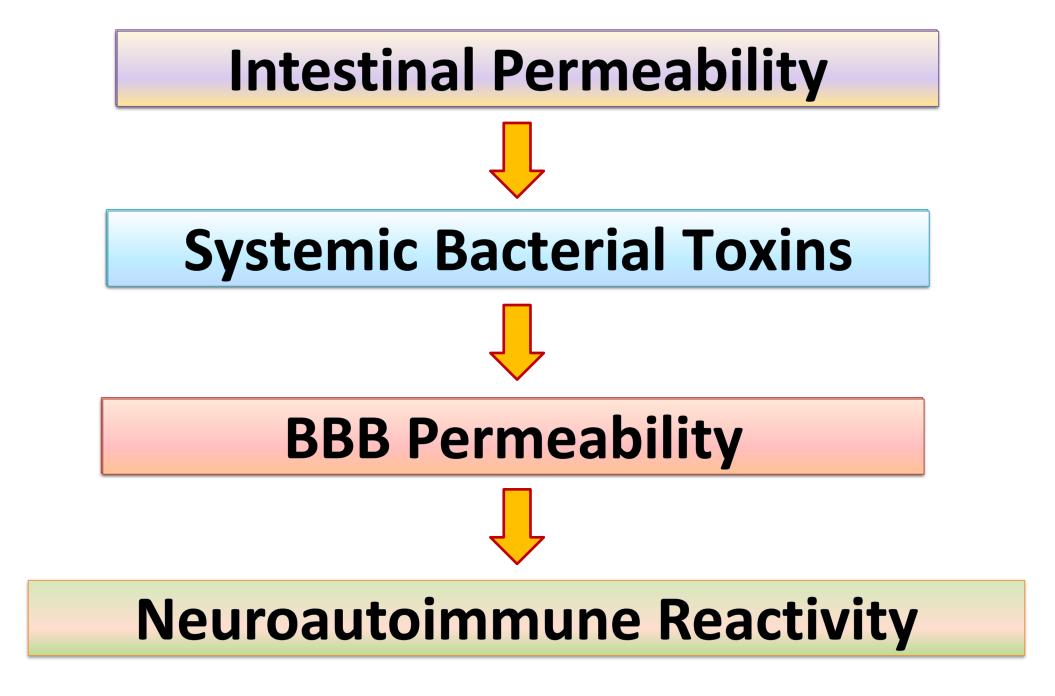
The Microbiota-Gut-Brain Axis



John FC, Kenneth JO, Caitlin SMC, et al. *Physiological Reviews*, October 2019;99(4):1877-2013



Ghaisas S, Maher J, Kanthasamy A. Gut microbiome in health and disease: Linking the microbiome-gut-brain axis and environmental factors in the pathogenesis of systemic and neurodegenerative diseases. *Pharmacol Ther*. 2016;158:52-62





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MUCOSAL IMMUNE ABNORMALITIES

IMBALANCED GUT FLORA

INTEST

You can PREVENT this

NEUROINVASION

NEURODEGENERATION

Alzheimer's/concussion/brain

Brain Benefits	1 tsp daily
Amyloid Benefits	3 caps daily
Neuro Benefits	3 cap daily
G.I. Benefits	1 scp bid
MegaProbiotic ND 50	1 cap daily







Gut health

G.I. Benefits	1 scp bid
Mega Probiotic ND 50	1 cap daily
Mega Probiotic for Her	1 cap daily
Liquid D3 10,000 IU	5 sprays daily
Clear G.I.	4 caps daily







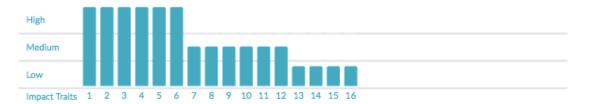




Health Action Plan

How These Traits Affect You

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Impact Traits	Impact	Learn More
1 Estrogen Metabolism	⊟нідн	Page 12
2 Glutathione	⊟ НІGH	Page 14
3 Inflammation	HIGH	Page 15
4 Oxidative Stress	Нібн	Page 17
5 SLC	HIGH	Page 18
6 SOD	⊟ ніgh	Page 19
7 CYP1B1	- MEDIUM	Page 20
8 CYP2s	- MEDIUM	Page 21
9 NAT	- MEDIUM	Page 22
10 Nrf2	- MEDIUM	Page 23
11 SULT	- MEDIUM	Page 24
12 UGT	- MEDIUM	Page 25
13 CYP1A1	LOW	
14 CYP1A2	LOW	
15 MTHFR	LOW	
16 SUOX	LOW	

The Liver Has Many Functions

The liver works in the body like an oil filter works in a car

Your Liver:

- Processes the body's stored sugar (glycogen)
- Converts the sugar you eat to usable energy
- Creates bile to aid in the digestion of fats
- Removes hormones (estrogens, epinephrine)
- Converts thyroid hormones
- PRIMARY DETOXIFICATION ORGAN



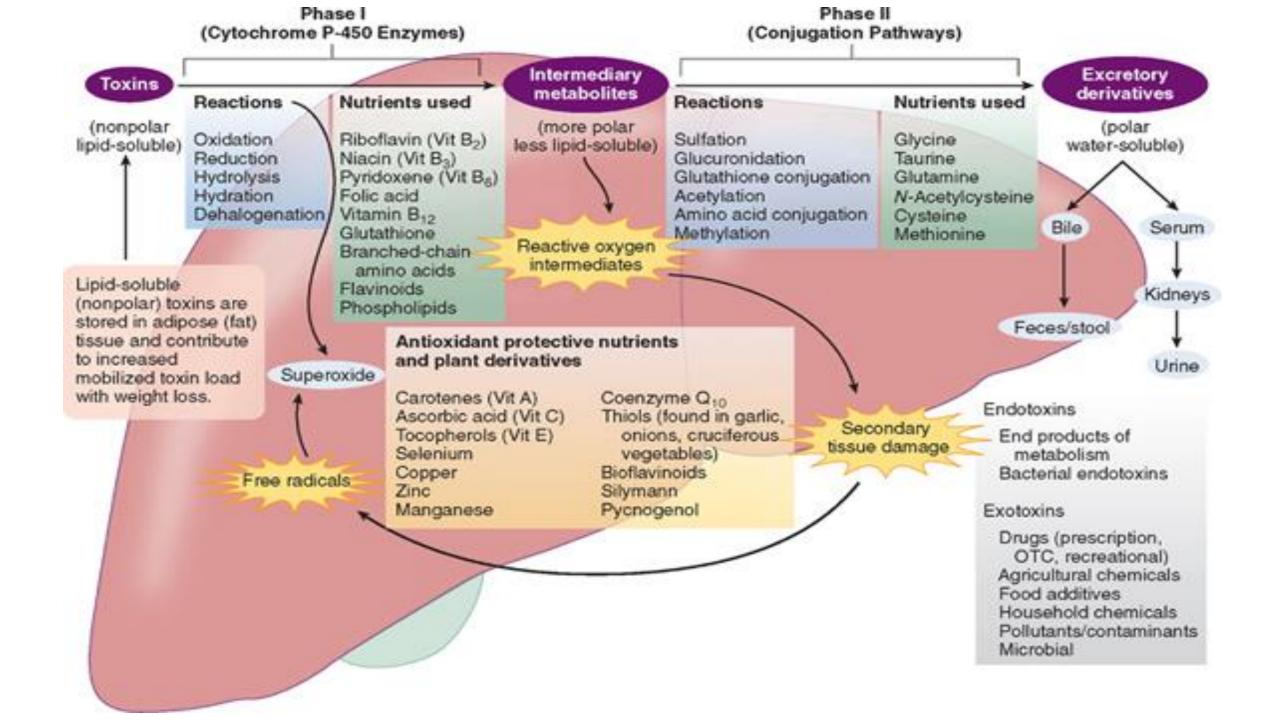
Remember...

- How well our body detoxifies determines our susceptibility to disease
- If we take in toxins quicker than our body can get rid of them, we are in trouble
- Toxic overload is a silent killer

Your liver is your 3rd brain

- Fights off infections
- Neutralizes toxins
- Helps to clot blood
- Controls blood glucose level
- Breaks proteins down into amino acids
- Produces cholesterol
- Produces bile
- Produces its own protein

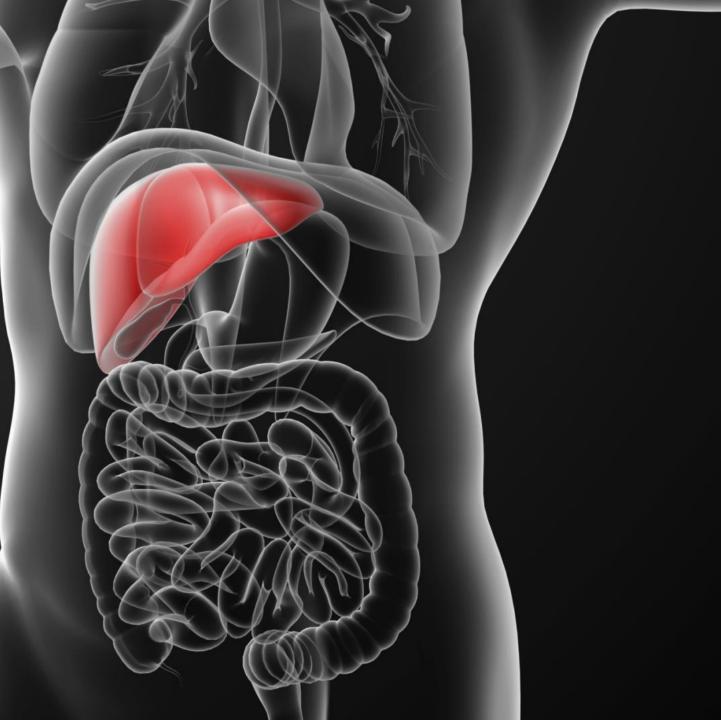




Phase II Pathways

- Sulfation toxins attach with sulfur compounds. Primary cortisol pathway
- **Glucuronidation** glucuronic acid combines with toxins. Primarily aspirin pathway
- **Glutathione conjugation** the attachment of glutathione to toxins to detoxify fat soluble toxins
- Acetylation acetyl co-a is attached to toxins
- Amino acid conjugation conjugation of toxins with amino acid xenobiotics
- Methylation involves conjugating methyl groups to toxins. **estrogen**

The body's natural detoxification pathways to eliminate harmful chemicals and toxins may benefit from additional support



Detox panel

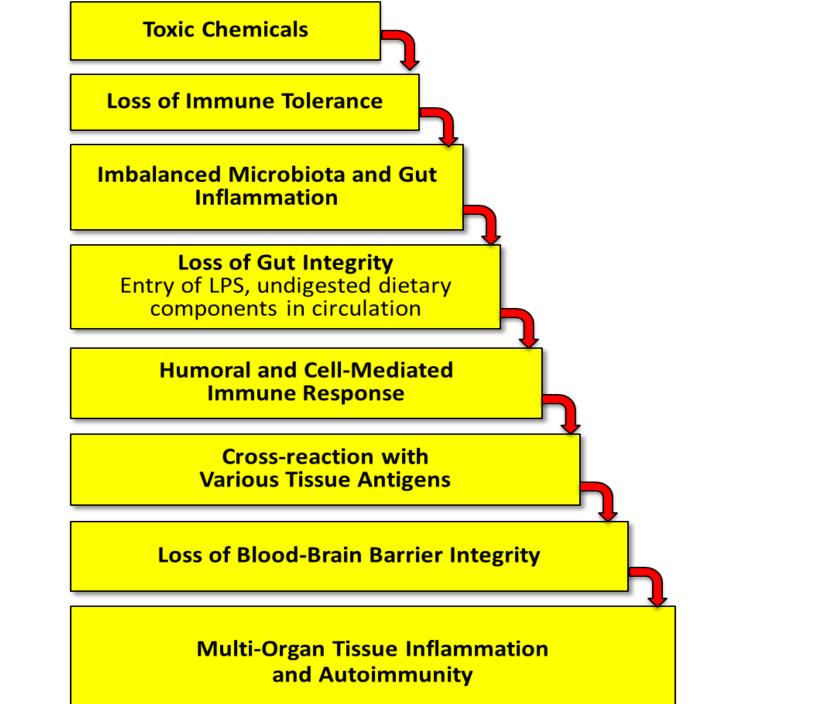
G.I. Benefits	1 scp bid
MegaProbiotic ND 50	1 cap daily
Enzyme Benefits	1 cap per meal
Detox Benefits	6 caps per day



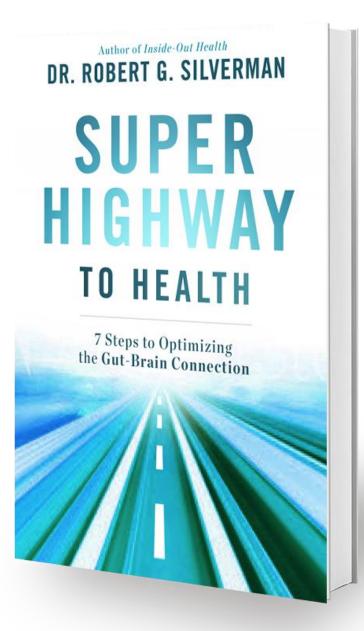






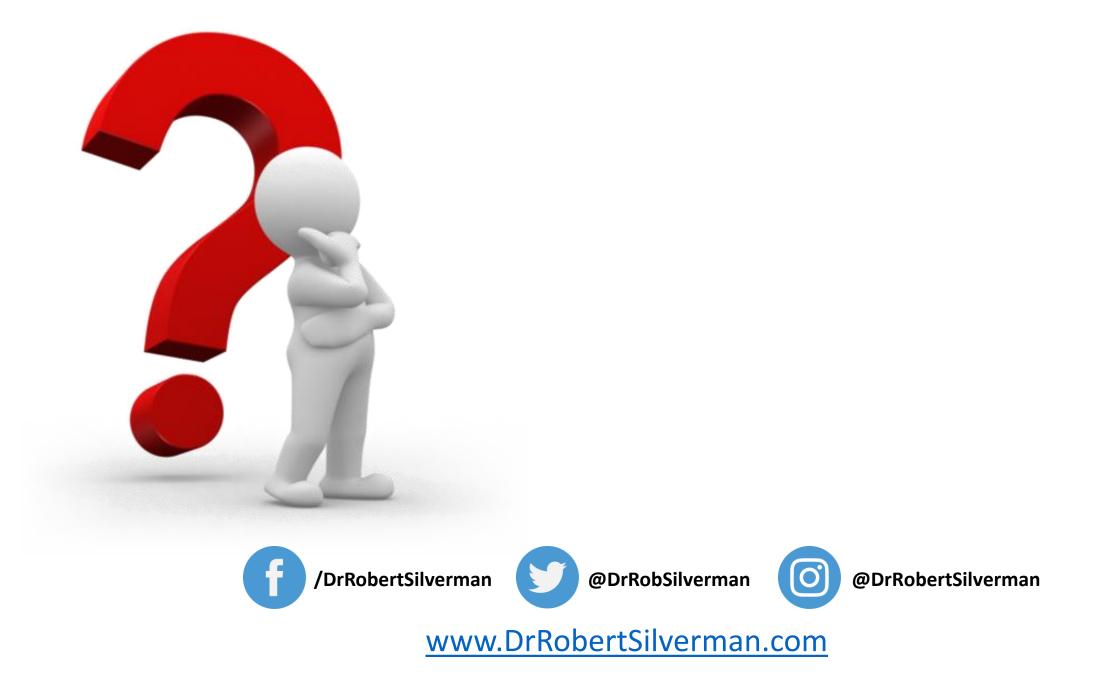


Keep an eye out...

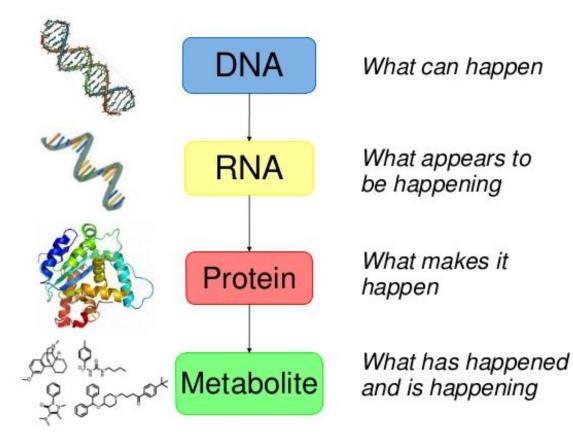


"Take care of your body, it's the only place you have to live".

Jim Rohn

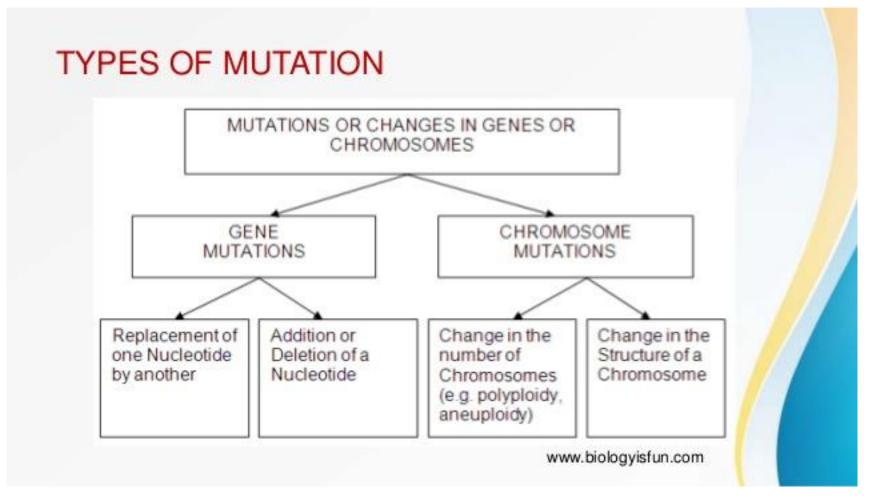


The central dogma of biology



Mutation vs. Variation

- Chromosomal mutation: permanent change in chromosome which changes the DNA sequence
 - Section of chromosome that includes multiple genes
 - Affect structure
 - Number
- Gene variation (mutation): change in part of the nucleotide sequence
 - Increases genetic variation
 - Different versions of the same gene

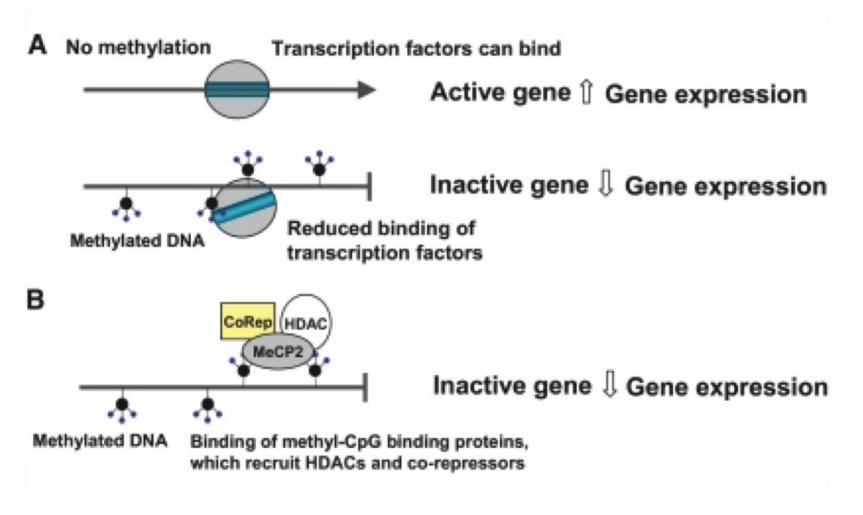


Impact of SNPs

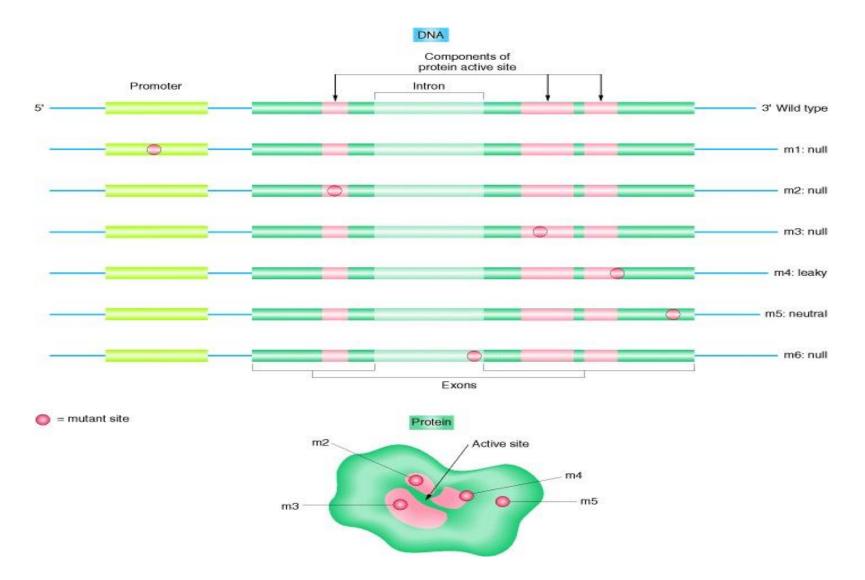
• Most have no impact on health

Impact on Health and Development	Example	
Response to drugs	CYP2D6 effects morphine metabolism	
Susceptibility to environmental factors	GSTM binds to toxins	
Response to dietary factors	BCOM1 converts beta-carotene to vitamin A	
Response to exercise factors	ACE associated with increased endurance ability	

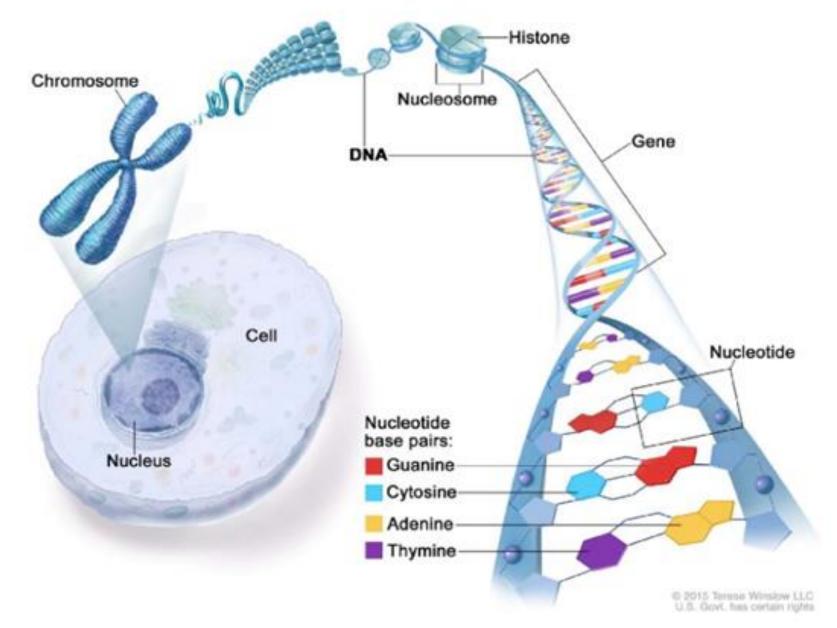
DNA Methylation



Downstream Effects of Variants

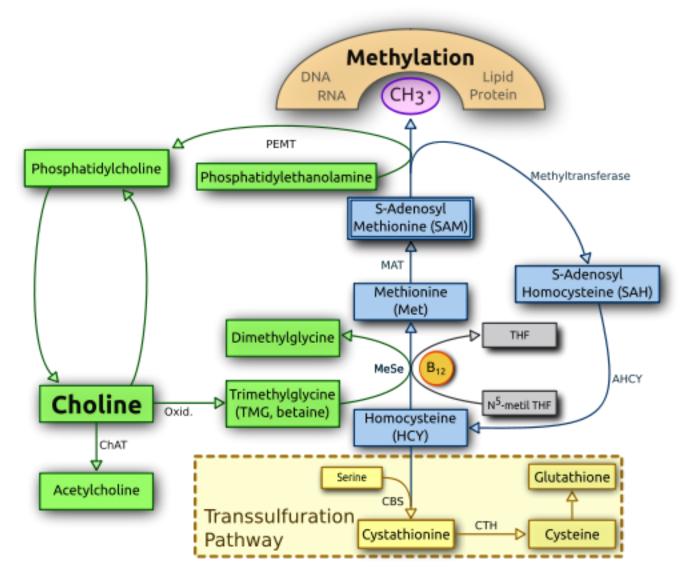


DNA Structure



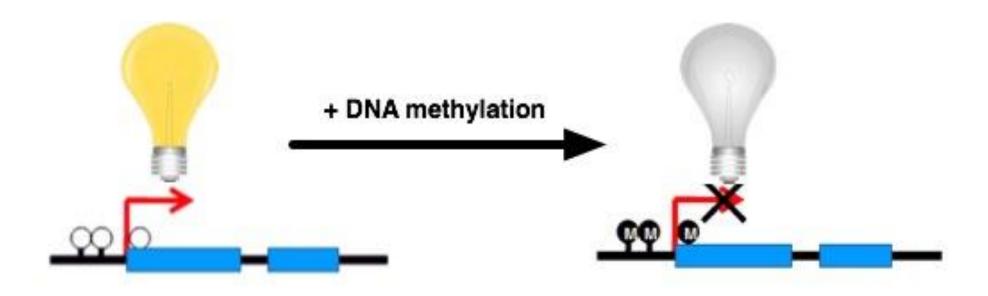
https://humanoriginproject.com/dna-full-form/

Effect Of SNPs On Methylation



https://upload.wikimedia.org/wikipedia/commons/thumb/c/c8/Choline metabolism-en.svg/500px-Choline metabolism-en.svg.png

DNA Methylation



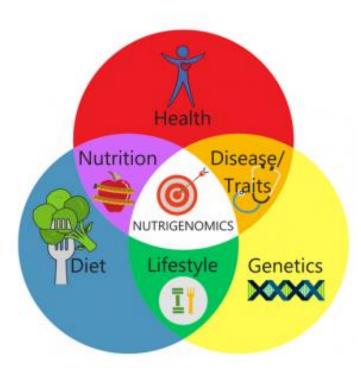
gene switched "on": transcription gene switched "off": no transcription

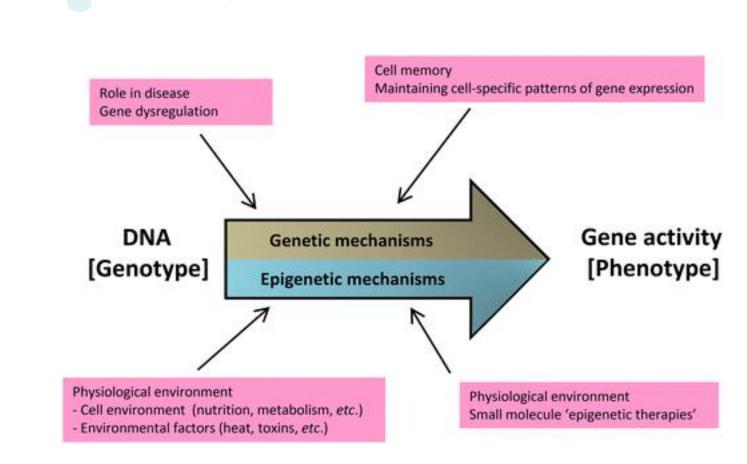
figure 1: Transcriptional silencing of gene promoters via DNA methylation

https://www.elitenetzwerk.bayern.de/uploads/tx_templavoila/Forschungsbericht_Epicombing_Zillner_figure1.jpg

Nutrigenomics

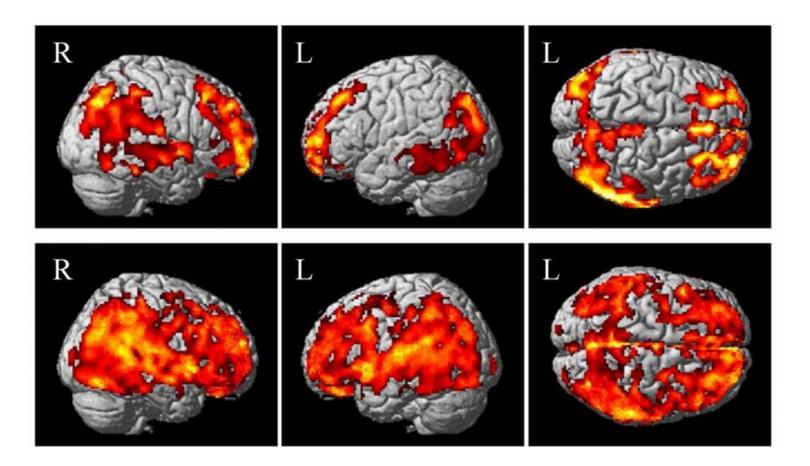
- SNPs largely influence our biochemical individuality
- Genetics study of genes and inheritance
- Genomics study of genes, their functions and interactions with each other and their environment
 - Epistasis interaction between difference genes
 - Epigenetics interaction between genes and the environment







APOE



https://3c1703fe8d.site.internapcdn.net/newman/gfx/news/hires/2015/impactofmajo.jpg

NIH funds clinical trials using genomics to treat chronic diseases



Credit: Ernesto Del Aguila III, NHGRI. High-resolution image on Flickr

July 24, 2020

Presence of Genetic Variants Among Young Men With Severe COVID-19

VILLILE FILLOF |

Caspar I. van der Made, MD^{1,2,3,4}; Annet Simons, PhD¹; Janneke Schuurs-Hoeijmakers, MD, PhD¹; <u>et al</u>

» Author Affiliations | Article Information

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CONTRACTOR

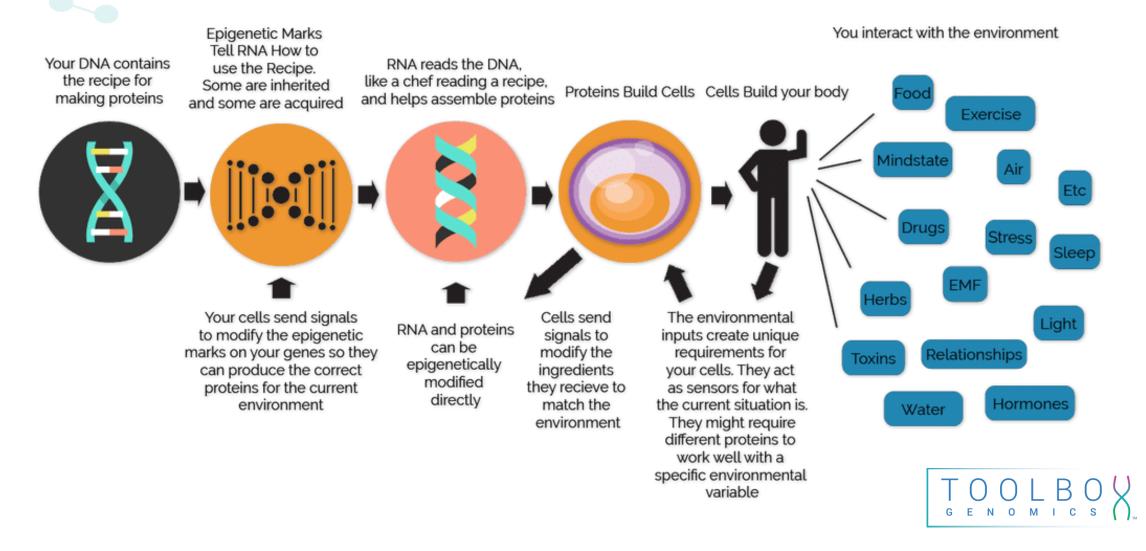
Dr. Rob Musculoskeletal Panel

Musculoskeletal Panel – designed to support three different groups: athletes, weekend warriors, or sedentary patients interested in increasing their exercise:

- Musculoskeletal Pain
- Disc Degeneration
- Muscle Damage
- Vitamin D3
- Magnesium
- Vitamin C
- Muscle Fiber Type

What Is Epigenetics?

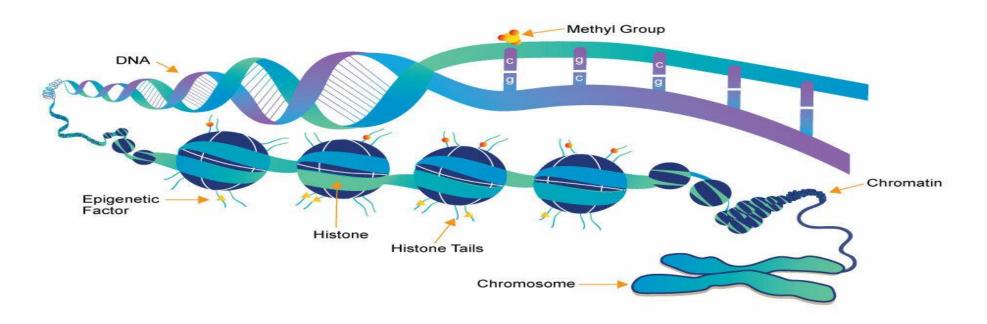
Epigenetics is the feedback loop between our genes and the environment. Our cells are constantly updating our genes on what they need to thrive. By inputting the correct environmental variables for your genes, food included, we can create health, longevity, and leave benficial epigenetic marks for the next generation. Epigenetic coaching is all about optimizing the inputs to your system.



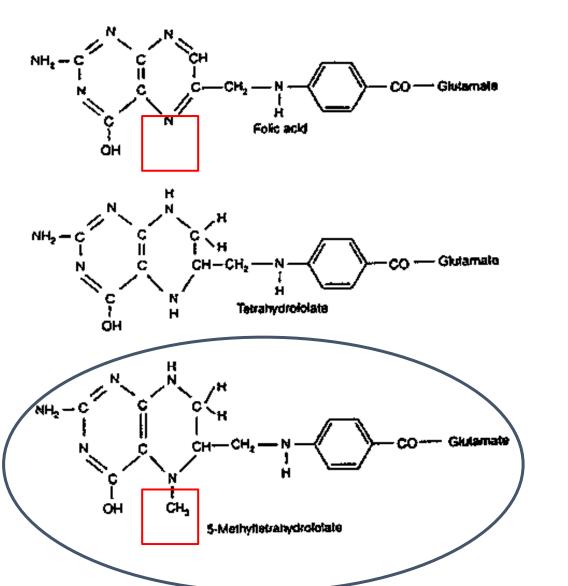
Epi: "at or upon"

Epigenetics: changes to our DNA that changes the expression

- Methylation
- Histone modification
- MicroRNA



Ways To Support MTHFR



Use 5-MTHF supplements



https://mk0dietvsdiseascuno2.kinstacdn.com/wp-content/uploads/2016/02/folic-acid-tetrahydrofolate-and-5-MTHF-structure.png

10 ways to



- 1) Hit the books
- 2) Butt out
- 3) Follow your heart
- 4) Heads up
- 5) Fuel up right

- 6) Catch some ZZZzzz
- 7) Take care of your mental health
- 8) Buddy up
- 9) Stump yourself
- 10) Break a sweat