DNA-targeted Precision Medicine Using a Genomic Clinical Decision Support Tool

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Founder & CEO
Lile Wellness Partners

OPA Annual Conference & Trade Show
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Disclosure Statement

Dr. Laura Lile has no relevant financial relationship(s) with ineligible companies to disclose.

None of the planners for this activity have relevant financial relationships with ineligible companies to disclose.

Learning Objectives

At the completion of this activity, the participant will be able to:

1. Explain the broad application of genomics as a prevention and intervention strategy;

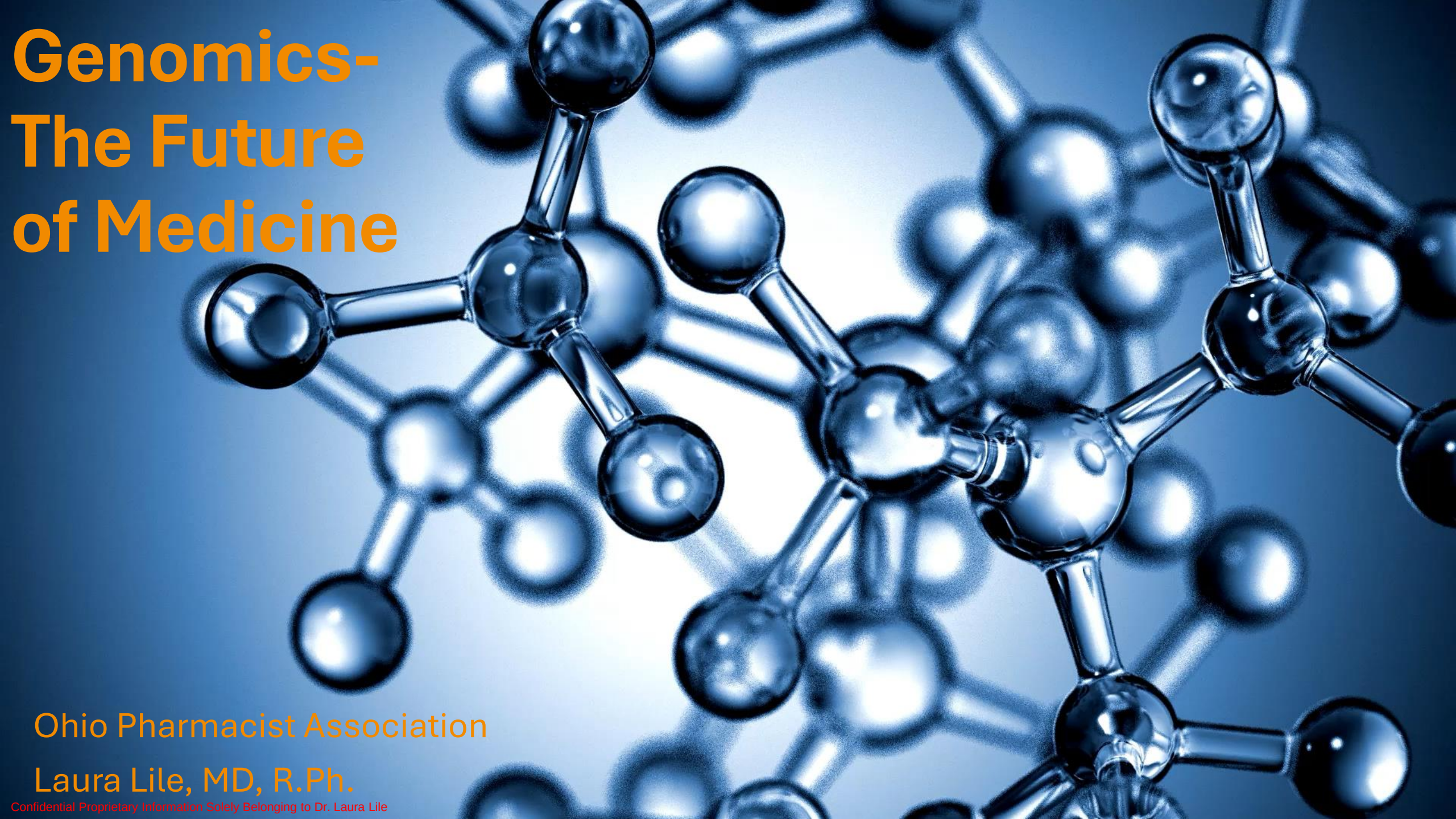
2. Illustrate the importance of pharmacists in genomics; and

3. Recognize how pharmacists can consult with complex patients through genomic testing.

Today's Agenda

1. Pharmacogenomics vs Root Cause Genomics
2. Case One- Optimizing Anti-depressant Therapy
3. Introduction to Cognition Genomics
4. Case Two- Rachel – APOE 3/3

Genomics- The Future of Medicine



Ohio Pharmacist Association

Laura Lile, MD, R.Ph.

Meet The Doctor

Laura Lile M.D., R.Ph.

- Lile Wellness Partners - Founder & CEO
- Island Compounding Pharmacy - Founder & CEO

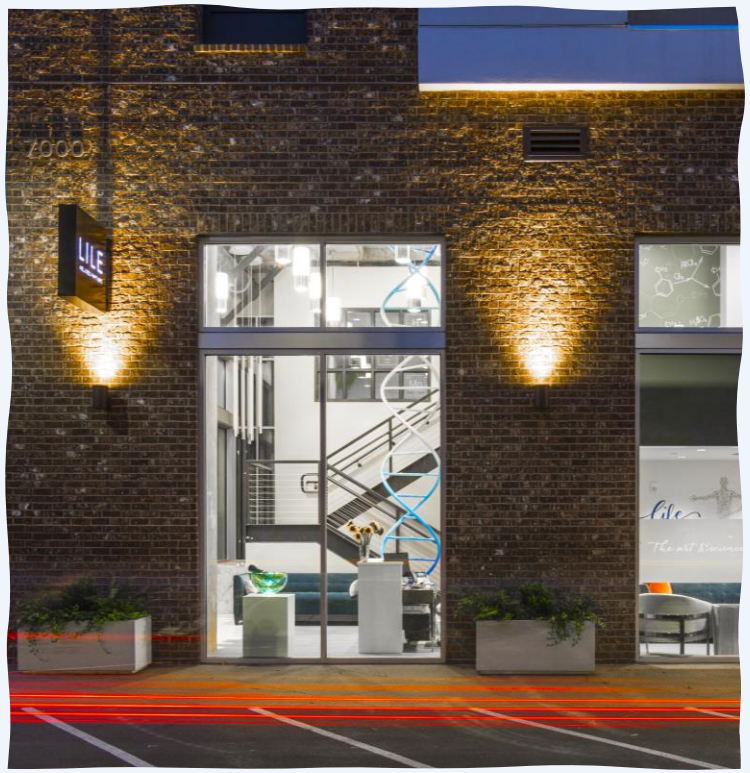
Dual credentialed and board certified as a Registered Pharmacist and MD

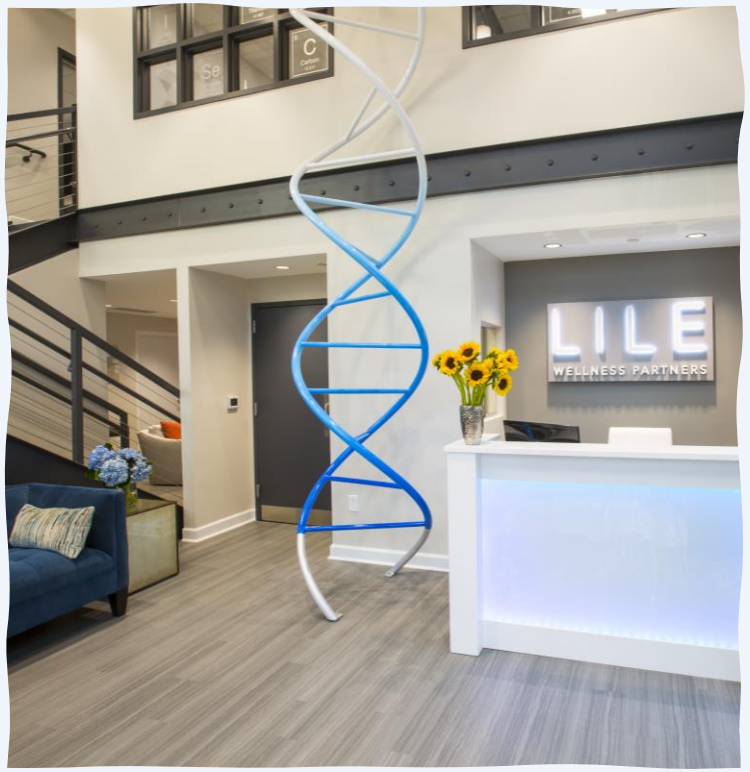
OSU COP 1987 – BSPharm, R.Ph.

Opened one of the first drive-thru pharmacies in the Midwest at the age of 25

Medical practice focuses on proactive, preventative healthcare with an emphasis on longevity and epigenetics.

Supports future pharmacists through mentoring and advocating for pharmacists to be credentialed to provide genomic consultations.





Genomics are in my DNA!

Epigenetics

The instructions for life, housed in our **DNA, can not be changed**. We are born with the same genetic profile that we will keep our entire life

This makes some people more **innately susceptible to some diseases and advanced aging** compared to others. Dealing with the fixed nature of our genetics is like getting dealt a specific hand in a card game.

HERE IS THE GOOD NEWS!

While you can't change the cards you have been dealt, you can control how they are played!

Your **epigenetics can be significantly impacted by lifestyle factors** such as diet, use of medications and supplements physical activity, stress, environmental pollutants, and more.

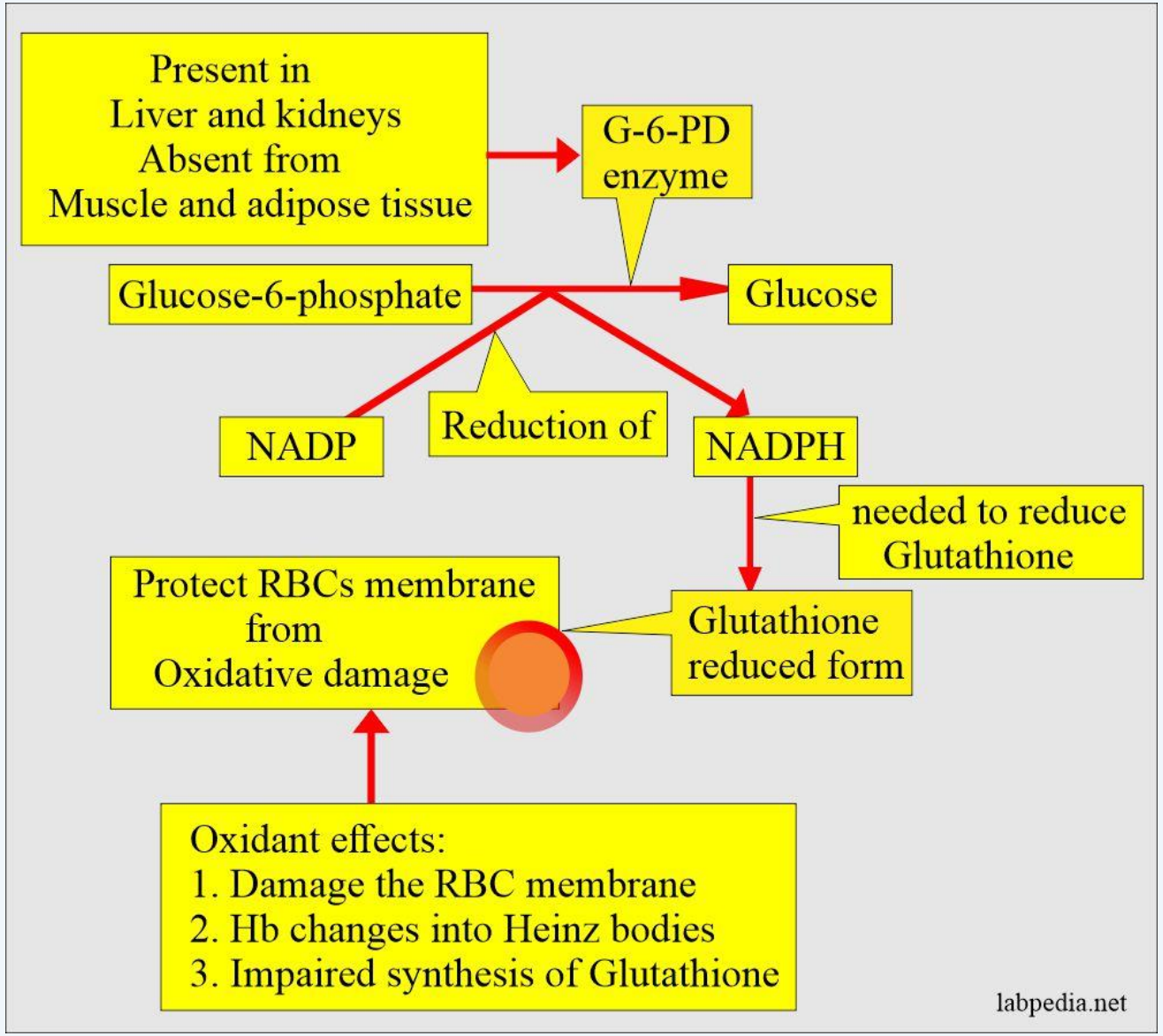
Changing your epigenetics is the most direct way to hack your DNA expression.

What is Pharmacogenetics?

- Pharmacogenetics is the study of how variation in a single gene can impact on variability in the body's response to one specific medicine (or group of medicines).
- Pharmacogenetics considers a person's genetic information regarding specific genes that control things, like how drugs are transported and metabolized by the body. Changes in these genes can affect how medicines function, making them effective or helping to predict which patients are more likely to suffer side effects.
- The goal of pharmacogenetics is to use a patient's individual genetic information to inform the best choice and dose of medicine.

History of Pharmacogenetics

- The history of pharmacogenetics stretches as far back over 2000 years, when it was noted that ingestion of fava beans resulted in a potentially fatal reaction in some, but not all, individuals.
- It was not until 1950s that some enzyme polymorphisms (G6PD) were discovered



Origins of Pharmacogenetics

DR. ARNO MOTULSKY (1957)

Refined the concept that inherited defects of metabolism could explain individual differences in drug response

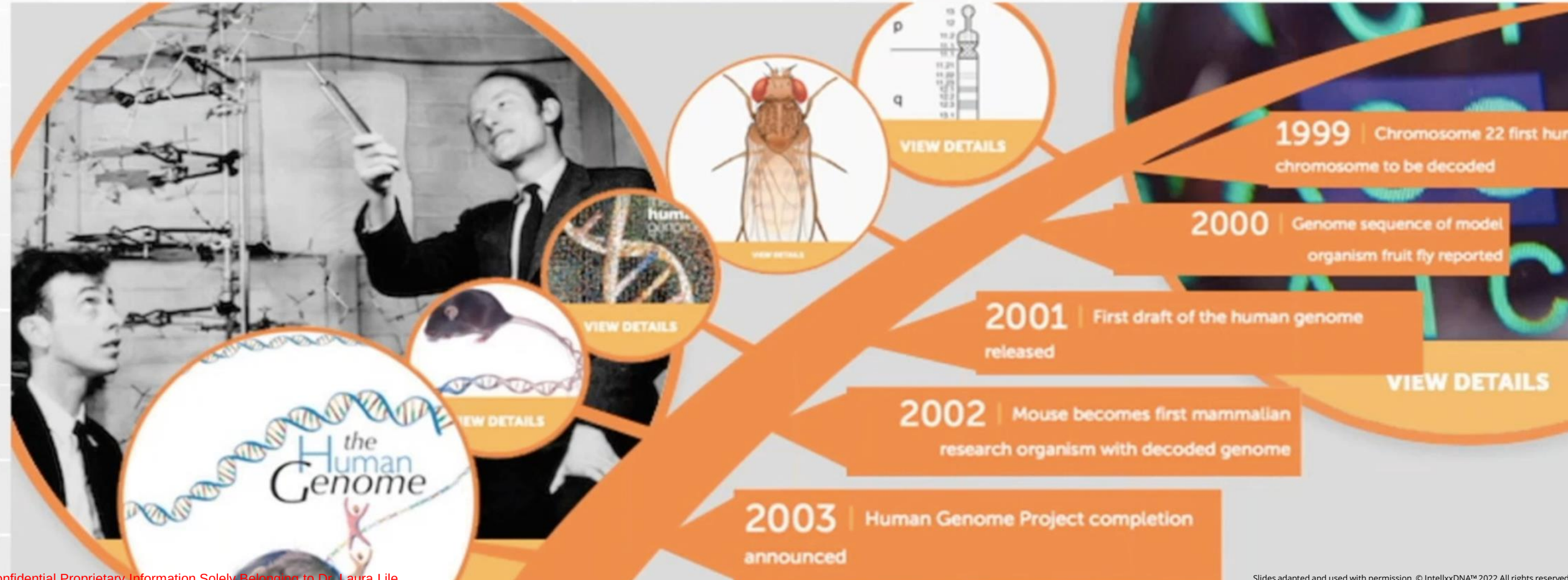
DR. FRIEDRICH VOGEL (1959)

Coined the term "Pharmacogenetics"

DR. ELLIOT VESELL (1968)

Showed remarkable similarities of drug disposition in identical twins vs fraternal twins

1953 – DNA Helix
2003 – Genome Sequencing
2021 – YOUR DNA IS USEFUL AND CAN HELP YOU OPTIMIZE HEALTH



What is Pharmacogenomics?

- Pharmacogenomics is the study of how a patient's genome can influence how they respond to medicines
- Pharmacogenomics is like pharmacogenetics, except that it typically involves the search for variations in multiple genes that are associated with variability in drug response.
- **Pharmacogenomics** can examine the entirety of the genome, rather than just single genes, and can examine genetic variation among large groups of people within the population, for example to see how different drugs might affect different ethnic groups.

Why are **Genomics** important to our health?

- Genomics helps researchers understand why one person gets sick and another doesn't with the same exposures.

- Apart from accidents, in 9 out of 10 leading causes of death, genomics factor in (heart disease, diabetes, etc.)

Data are for the U.S.

Number of deaths for leading causes of death

- Heart disease: 695,547
- Cancer: 605,213
- COVID-19: 416,893
- Accidents (unintentional injuries): 224,935
- Stroke (cerebrovascular diseases): 162,890
- Chronic lower respiratory diseases: 142,342
- Alzheimer's disease: 119,399
- Diabetes: 103,294
- Chronic liver disease and cirrhosis : 56,585
- Nephritis, nephrotic syndrome, and nephrosis: 54,358

Source: Mortality in the United States, 2021, data table for figure 4

Note: Final data for 2021. Provisional data for 2022 and 2023 are available through CDC Wonder.

Sample Pharmacogenomic report

GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

Patient, Sample
DOB: 7/22/1984
Order Number: 219
Report Date: 8/5/2020
Clinician: Sample Clinician
Reference: 1456CIP

Questions about report interpretation?
Contact our Medical Information team
855.891.9415
medinfo@assurexhealth.com

ANTIDEPRESSANTS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION	
desvenlafaxine (Pristiq®)	**trazodone** (Desyrel®)	1	**selegiline** (Emsam®)	2
levomilnacipran (Fetzima®)	**venlafaxine** (Effexor®)	1	**mirtazapine** (Remeron®)	1,6
vilazodone (Viibryd®)	**fluoxetine** (Prozac®)	1,4	**sertraline** (Zoloft®)	2,4
	bupropion (Wellbutrin®)	1,6	**amitriptyline** (Elavil®)	3,8
	citalopram (Celexa®)	3,4	**clomipramine** (Anafranil®)	1,6,8
	escitalopram (Lexapro®)	3,4	**desipramine** (Norpramin®)	1,6,8
			doxepin (Sinequan®)	1,6,8
			duloxetine (Cymbalta®)	1,6,8
			imipramine (Tofranil®)	1,6,8
			nortriptyline (Pamelor®)	1,6,8
			vortioxetine (Trintellix®)	1,6,8
			fluvoxamine (Luvox®)	1,4,6,8
			paroxetine (Paxil®)	1,4,6,8

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PATIENT GENOTYPES AND PHENOTYPES

PHARMACOKINETIC GENES (PK)

CYP1A2 — **Extensive (Normal) Metabolizer**
*1/*1

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

CYP2B6 — **Extensive (Normal) Metabolizer**
*1/*1

CYP2B6*1 allele enzyme activity: Normal
CYP2B6*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

CYP2C19 — **Ultrarapid Metabolizer**
*17/*17

CYP2C19*17 allele enzyme activity: Increased
CYP2C19*17 allele enzyme activity: Increased

This genotype is most consistent with the ultrarapid metabolizer phenotype. This patient may have increased enzyme activity as compared to individuals with the normal phenotype.

CYP2C9 — **Intermediate Metabolizer**
*1/*2

CYP2C9*1 allele enzyme activity: Normal
CYP2C9*2 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

CYP2D6 — **Poor Metabolizer**
*10/*10

CYP2D6*10 allele enzyme activity: Reduced
CYP2D6*10 allele enzyme activity: Reduced

This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

CYP3A4 — **Extensive (Normal) Metabolizer**
*1/*1

CYP3A4*1 allele enzyme activity: Normal
CYP3A4*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

UGT1A4 — **Extensive (Normal) Metabolizer**
*1/*1

UGT1A4*1 allele enzyme activity: Normal
UGT1A4*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype. The patient is expected to have normal enzyme activity.

UGT2B15 — **Intermediate Metabolizer**
*2/*2

UGT2B15*2 allele enzyme activity: Reduced
UGT2B15*2 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

Sample Pharmacogenomic report

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COMBINATORIAL PHARMACOGENOMIC TEST

genesight

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PATIENT GENOTYPES AND PHENOTYPES

PHARMACODYNAMIC GENES (PD)

SLC6A4 — **Reduced Response**
S/S

This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the homozygous long promoter allele. The patient may have a decreased likelihood of response to selective serotonin reuptake inhibitors due to the presence of the short form of the gene and may benefit from medications with an alternative mechanism of action.

HTR2A — **Increased Sensitivity**
G/G

This individual is homozygous variant for the G allele of the -1438G>A polymorphism for the Serotonin Receptor Type 2A. They carry two copies of the G allele. This genotype has been associated with an increased risk of adverse drug reactions with certain selective serotonin reuptake inhibitors.

HLA-B*1502 — **Lower Risk**
Not Present

This patient does not carry the HLA-B*1502 allele or a closely related *15 allele. Absence of HLA-B*1502 and the closely related *15 alleles suggests lower risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

HLA-A*3101 — **Higher Risk**
T/T

This patient is homozygous for the T allele of the rs1061235 A>T polymorphism indicating presence of the HLA-A*3101 allele or certain HLA-A*33 alleles. This genotype suggests a higher risk of serious hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms when taking certain mood stabilizers.

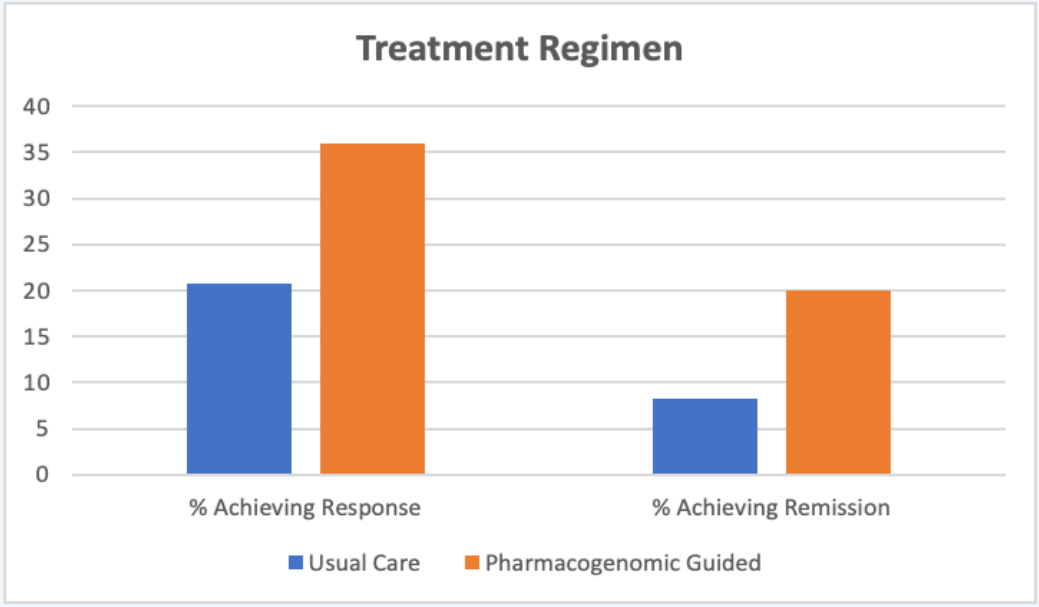
A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder

Joel G Winner [1], Joseph M Carhart, C Anthony Altar, Josiah D Allen, Bryan M Dechairo

Results Interpreted: The percent improvement in depressive symptoms was higher for the GeneSight group over TAU (30.8% vs 20.7%; p=0.28). TAU subjects who had been prescribed medications at baseline that were contraindicated based on the individual subject's genotype (i.e., red bin) had almost no improvement (0.8%) in depressive symptoms measured by HAMD-17 at week 10, which was far less than the 33.1% improvement (p=0.06) in the pharmacogenomic guided subjects who started on a red bin medication and the 26.4% improvement in GeneSight subjects overall (p=0.08).

Conclusions: Pharmaco-genomic-guided treatment with GeneSight doubles the likelihood of response in all patients with treatment resistant depression and identifies 30% of patients with severe gene-drug interactions who have the greatest improvement in depressive symptoms when switched to genetically suitable medication regimens.

2013 PGX study only 20% of Individuals Achieved Remission at 10 Weeks – Double Blind Randomized



This means 70-80% of individuals did not achieve remission – which implies medications being used were not fully addressing underlying conditions

Winner J. et al 2013

Cost of uncontrolled depression on the US Healthcare System

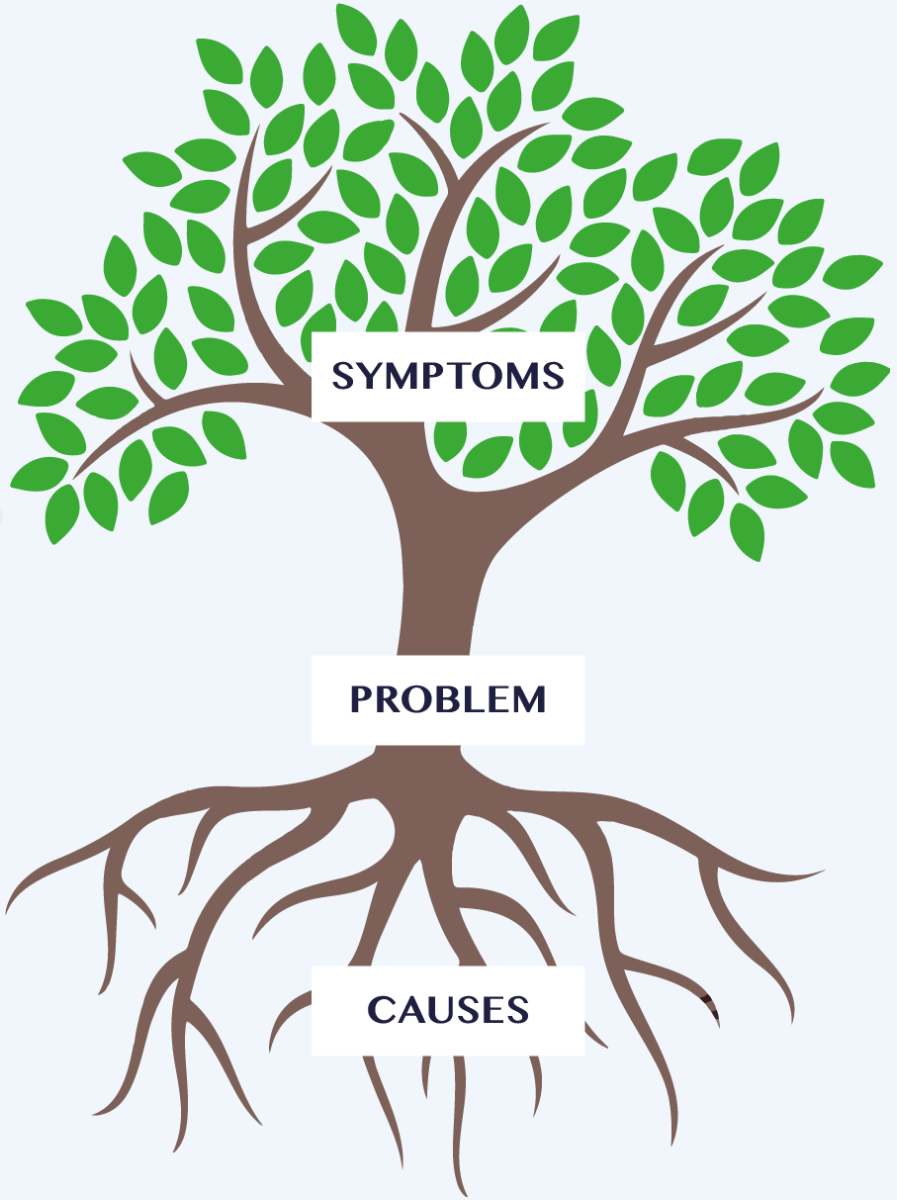
Depression costs U.S. employers approximately $187.8 billion a year. This includes:

$134 billion in health care (health and mental health combined)

$20.9 billion in absenteeism

$32.9 billion in lost productivity.

What are we missing?



Above the surface you can see the **symptoms** of the problem

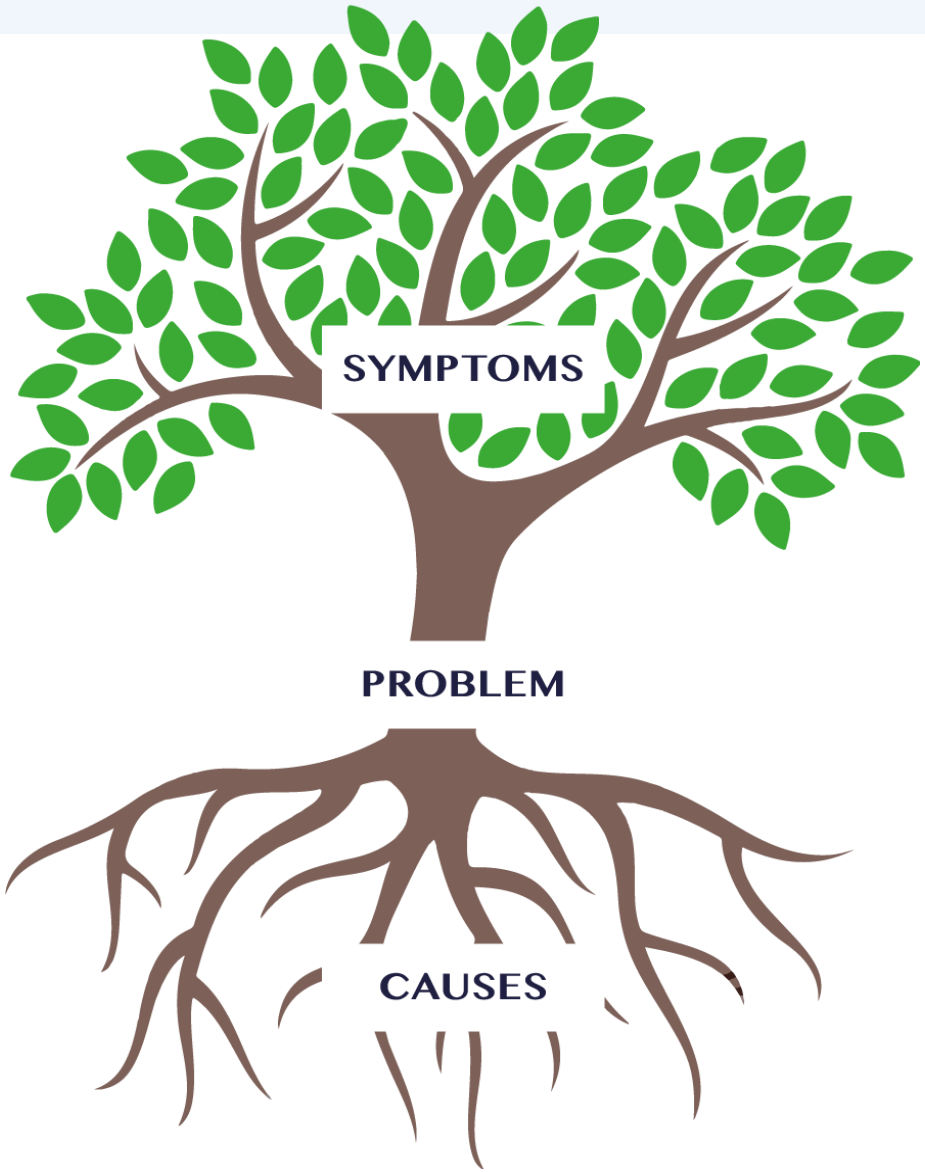
Dig deeper and you find the **root cause** of the problems

Root cause genomics!

The Future of Medicine: Root Cause Genomics

Root cause genomics applies to chronic diseases including:

- Mental Wellness
- Alzheimer and Dementia
- Hypertension
- Diabetes
- Autoimmunity
- Autism
- Cardiovascular disease

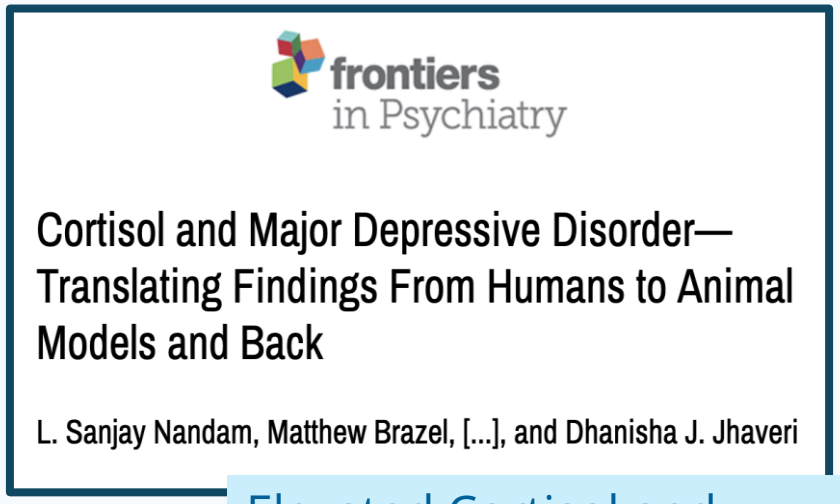


Markers of oxidative stress were almost 5x higher in individuals with depression compared to controls.

Next Generation Genomics:

Must Address Wide Breadth of Root Causes

The next generation of genomic tools provides the ability to identify root causes of depression and potentially help patients AVOID the need for anti-depressants or decrease their use and most importantly feel optimally

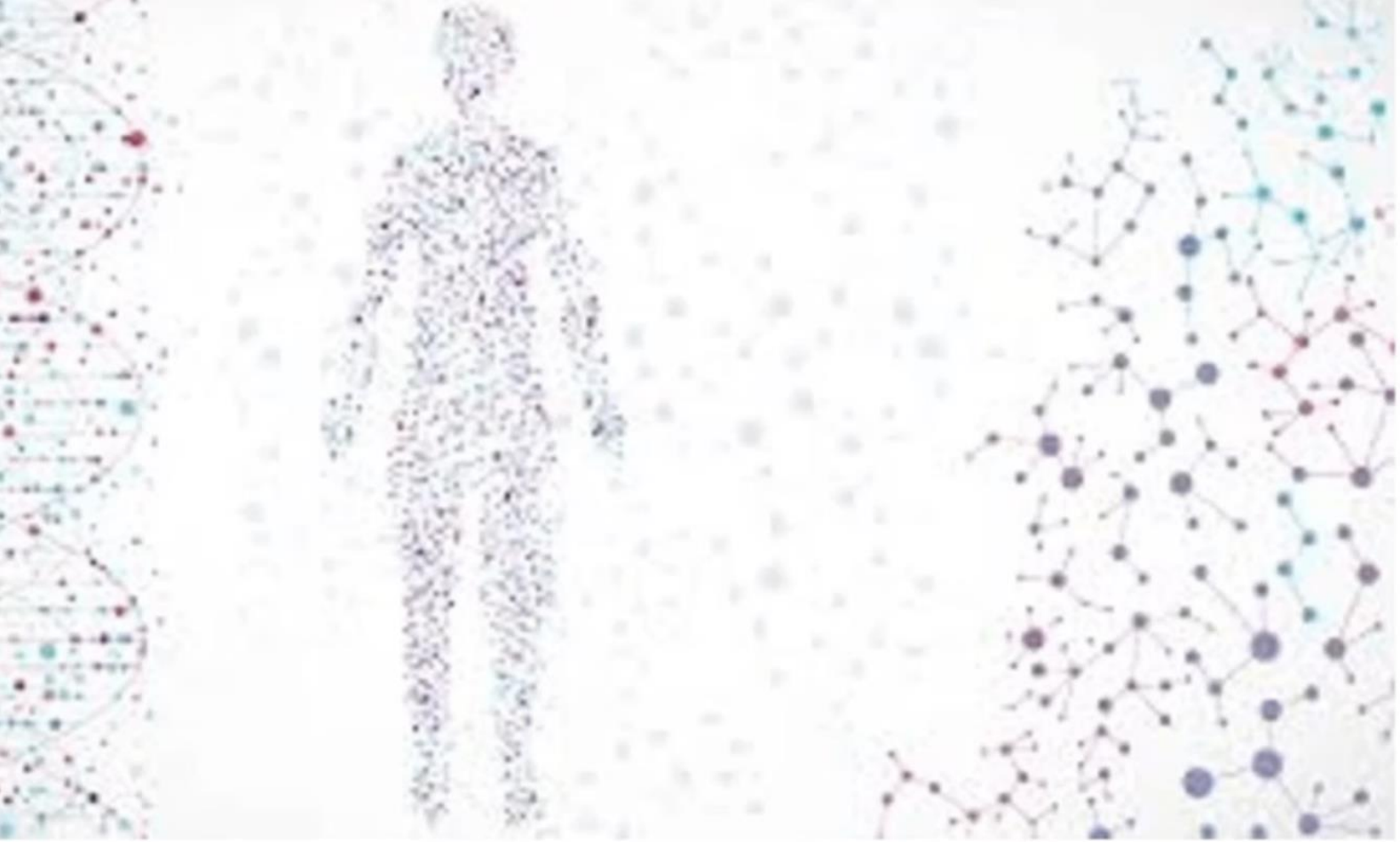


Elevated Cortisol and Adrenaline all contribute to depression.

Inflammation has a significant role in depression – multiple different kinds of inflammation.

Without a Clinical Support Tool, genetic information can be overwhelming to interpret

Liver Detox - Phase I (Figure 1)				
SNP ID	SNP Name	Risk Allele	Your Alleles	Your Results
rs1048943	CYP1A1*2C A4889G	C	TT	-/-
rs1799814	CYP1A1*4 C2453A	T	GG	-/-
rs2470890	CYP1A2 1545T>C	C	TT	-/-
rs2472304	CYP1A2*1F	A	AA	+/+
rs762551	CYP1A2*1F C164A	C	AA	-/-
rs2069526	CYP1A2*1K -739T>G	G	TT	-/-
rs28399424	CYP1A2*6 R431W	T	CC	-/-
rs1056836	CYP1B1 L432V	C	CC	+/+
rs1800440	CYP1B1 N453S	T	TT	+/+
rs9282671	CYP1B1 T241A	A	AA	+/+
rs5031016	CYP2A6 T1412C	G	AA	-/-
rs28399454	CYP2A6 V365M	T	CC	-/-
rs1801272	CYP2A6*2 A1799T	T	AA	-/-
rs35303484	CYP2B6 A136G	G	AA	-/-
rs34097093	CYP2B6 C1132T	T	CC	-/-
rs8192719	CYP2B6 C26570T	T	CC	-/-
rs2279344	CYP2B6 G23280A	G	AA	-/-
rs7260329	CYP2B6 G29435A	G	AA	-/-
rs28399499	CYP2B6 I328T	C	TT	-/-
rs2279343	CYP2B6 L262A	G	AA	-/-
rs3745274	CYP2B6 Q172H	T	GG	-/-
rs8192709	CYP2B6 R22C	T	CC	-/-
rs3211371	CYP2B6 R487C	T	CC	-/-
rs1042389	CYP2B6 T1421C	C	CT	+/-
rs36079186	CYP2B6 T20715C	C	TT	-/-
rs2279345	CYP2B6 T23499C	T	CC	-/-
rs12767583	CYP2C19 C5709T	T	CT	+/-
rs4917623	CYP2C19 T106C	C	TT	-/-
rs4986894	CYP2C19 T98C	T	CT	+/-
rs12248560	CYP2C19*17 C806T	T	CC	-/-
rs4244285	CYP2C19*2 G681A	A	AG	+/-
rs17878459	CYP2C19*2B G276A	C	GG	-/-
rs4986893	CYP2C19*3 G636A	A	GG	-/-
rs28399504	CYP2C19*4 A5001G	G	AA	-/-
rs41291556	CYP2C19*8 T358C	C	TT	-/-
rs17884712	CYP2C19*9 G17784A	A	GG	-/-
rs1057909	CYP2C9 42612A>G	G	AA	-/-
rs1057911	CYP2C9 50298A>T	T	AA	-/-
rs4917639	CYP2C9 A6326C	C	AA	-/-
rs4086116	CYP2C9 C334T	T	CC	-/-
rs10509680	CYP2C9 G2337T	T	GG	-/-
rs4918758	CYP2C9 T1188C	C	CT	+/-
rs1934967	CYP2C9 T2674C	T	CC	-/-
rs28371685	CYP2C9*11 1003C>T	T	CC	-/-



Genomics is about Identifying and ADDRESSING SNPs

- Identifying which SNPs or “variants” in itself is not useful.
- Just like a lab test genomics is only useful if you then know to modify or address these SNPs.
- That is why having a clinical decision support tool is important– making genomics USEFUL

BDNF Pathway

Homocysteine and Methylation Pathway

Vitamin B12 Pathway

Vitamin B6 Pathway

Vitamin D Pathway

Magnesium Pathway

Copper and Zinc Pathway

Heavy Metals Detox & Glutathione Pathway

There are so many contributing factors to depression and mental wellness.

- Neurotransmitters
- Gut Health
- Inflammation
- Homocysteine
- Minerals

Epub 2014 Dec 3.

Role of the blood-brain barrier in the nutrition of the central nervous system

Patricia Campos-Bedolla [1], Fruzsina R Walter [2], Szilvia Veszelka [2], Mária A Deli [2]

Affiliations + expand

PMID: 25481827 DOI: 10.1016/j.arcmed.2014.11.018

Abstract

The blood-brain barrier (BBB) is a dynamic and complex interface between the blood and the central nervous system regulating brain homeostasis. Major functions of the BBB include the transport of nutrients and protection of the brain from toxic compounds. This review summarizes the most important transport pathways contributing to the nutrition of the brain. Carrier-mediated transport selectively delivers small molecules like sugars, amino acids, vitamins, and trace elements. Large biomolecules, lipoproteins, peptide and protein hormones cross the BBB by receptor-mediated transport. Active efflux transporters participate in the brain efflux of endogenous metabolites as well as toxins, xenobiotics and drugs. Dysfunction in the transport of nutrients at the BBB is described in several neurological disorders and diseases. The BBB penetration of neuroprotective nutrients, especially plant polyphenols and alkaloids, their potential

https://doi.org/10.3389/fphys.2020.00973

Transport of Amino Acids Across the Blood-Brain Barrier

Rosa Zaragozá*

Department of Human Anatomy and Embriology, School of Medicine, IIS INCLIVA, University of Valencia, Valencia, Spain

The blood-brain-barrier (BBB), present in brain capillaries, constitutes an essential barrier mechanism for normal functioning and development of the brain. The presence of tight junctions between adjacent endothelial cells restricts permeability and movement of molecules between extracellular fluid and plasma. The protein complexes that control cell-cell attachment also polarize cellular membrane, so that it can be divided into luminal (blood-facing) and abluminal (brain) sides, and each solute that enters/leaves the brain must cross both membranes. Several amino acid (AA) transport systems with different distributions on both sides of the BBB have been described. In a broad sense, there are at least five different systems of facilitative transporters and all of them are found in the luminal membrane. Some of these transporters are very specific for a small group of substrates and are located exclusively on the luminal side of the BBB. However, the two major facilitative carriers, system L and system y^+, are

Active Transport is Required Across the BBB – So Peripheral Levels May Not Reflect Brain Levels

Genomics Can Help You Understand Who Might Require Higher Levels of What Due to Less Efficient Transport

Chronic Diseases are ALWAYS Multifactorial

Anxiety

- Serotonin
- Adrenaline Receptors and Metabolism
- GABA production
- B6
- Processing of blood sugar
- Conversion of T4 to T3 in brain

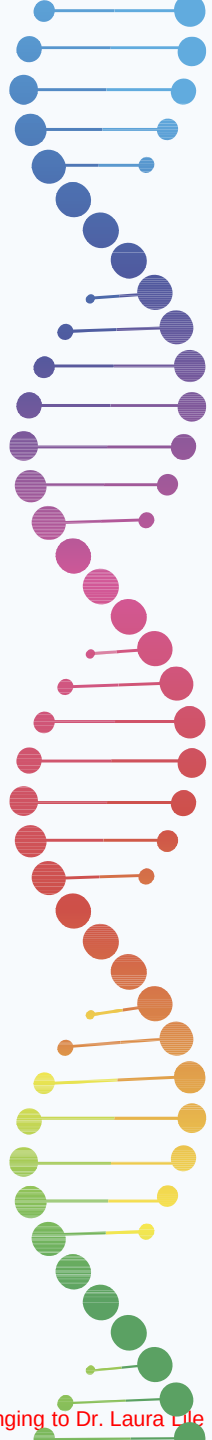
ADHD

- Neuronal connectivity
- Auditory Processing and speech center
- Dopamine
- Norepinephrine
- GABA

Depression

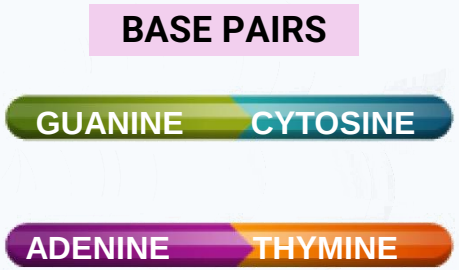
- Serotonin
- Adrenaline Pathways
- Methylation and homocysteine
- Cortisol
- Melatonin
- BDNF

Plus, gut health, inflammation, environmental exposures, nutrients are important for all health



Let’s talk **Root Cause** Genomics

SNPs are single nucleotide polymorphisms or base pair substitutions in your DNA



The building blocks of the DNA are base pairs.

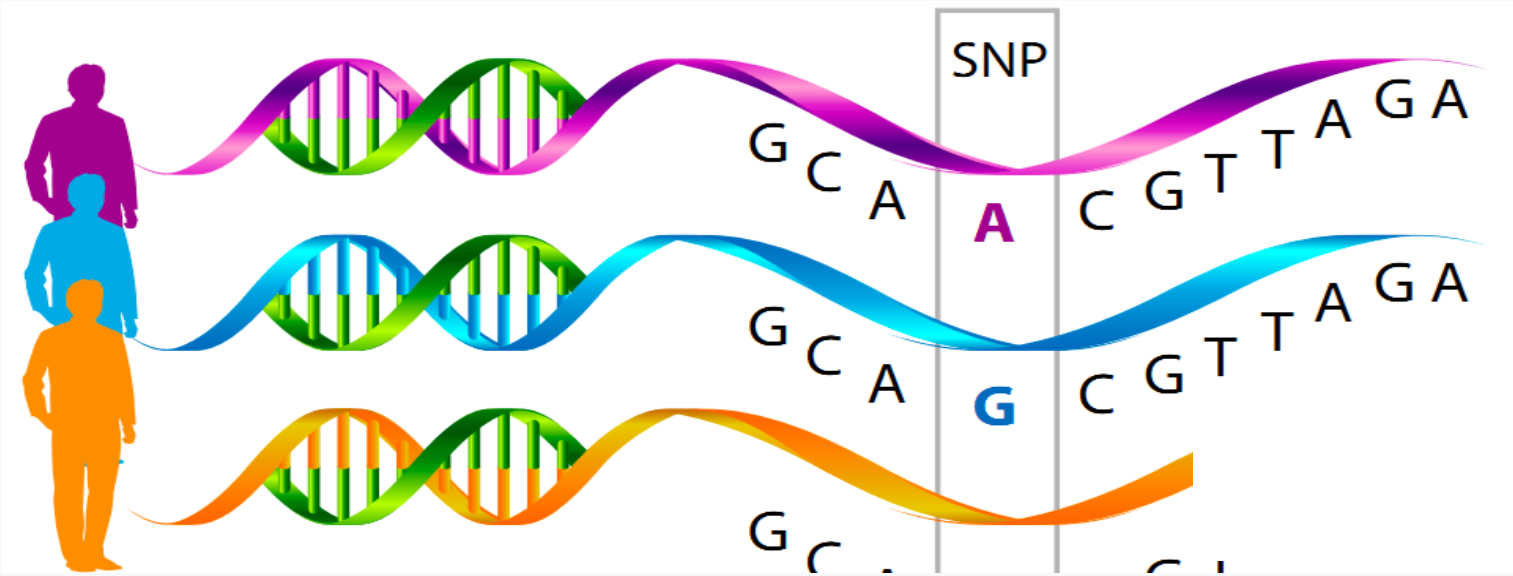
These building blocks are represented by letters **A**, **G**, **T** & **C**.

You have about ~3 billion of these letters in YOUR DNA.

Typically, about 1 million of these can vary – they are SNPS

SNP ▶ *Single Nucleotide Polymorphism:*

A change in one nucleotide within a stretch of DNA or within a gene



Case Study One:

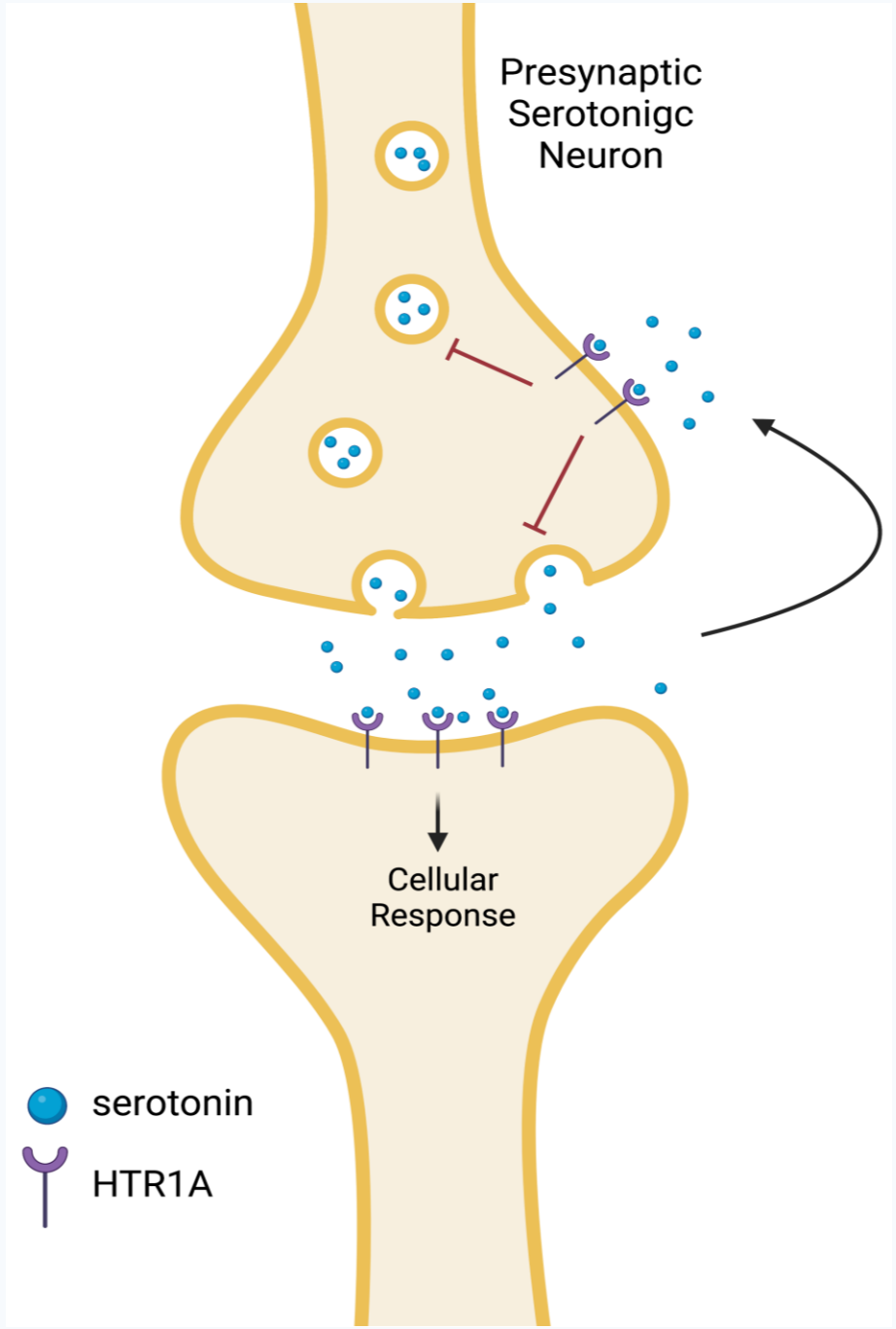
Optimizing Anti-Depressant Therapy

Case of Cathy

- 65-year-old, Retired
- Has been depressed since she was a teen and was told to “get over it” and cheer up.
- Also has IBS-D, migraines and ADHD
- Has been tried on SSRIs and does ok on sertraline 150 mg – but never in remission. PHQ9 score of 13
- Likes to garden and canning vegetables and being with her grand children.

Cathy's Depression Genomics Had **Serotonin** Components

Risk **SNP**	Gene **Risk allele**	Patient **Allele**	Variant (0, 1, 2)	Notes
rs79…	HTR1A G 28.9%	GC	1	5-Hydroxytryptamine Receptor 1A (lower serotonin signaling): • Even one copy of this gene variant is associated with 2.8 x the risk of depression and anxiety • Associated with lower response to antidepressants. Potential Interventions: 5-HTP extended release, SAMe, Saffron, exercise, bright light
rs62..	HTR2A A 40.9%	AG	1	5-Hydroxytryptamine Receptor 2A (lower GABA, higher cortisol, and lower serotonin) Higher HTR2A is associated with higher cortisol and lower GABA, which contributes to depression. Potential interventions: Increased response to citalopram and potentially other SSRIs. L-theanine and adaptogens like Magnolia officinalis, ashwagandha and rhodiola to lower cortisol may also be of benefit.
rs62,,	BDNF T 31.1%	TC	1	BDNF: Brain Derived Neurotrophic Factor (lower BDNF) This SNP is associated with lower conversion of proBDNF to the mature form • CT associated with 1.67 x risk depression • TT associated with 2.58 x risk of depression Potential Interventions: intense exercise, green coffee bean extract, hericeum erinaceus, high butyrate diet. SEE HANDOUT for other BNDF interventions.



HTR1A: Serotonin Sensor

HTR1A receptors are regulators. They are meant to stop serotonin production and release when synaptic serotonin levels are high.

Variant is associated with increase in presynaptic expression and overactive down-regulation.

Thus, HTR1A Turns off serotonin synthesis even when the levels are not high enough.

HTR1A Downregulates the Production and Release of Serotonin

With the variant, you have an OVERACTIVE Regulator where serotonin binds too tightly, and your body acts as if you have a lot more serotonin than you have.

- HTR1A has been associated with **2.82 x the risk of depression and anxiety**
- **These SNPs have nothing to do with drug metabolism, so they are often not included in PGX.**
- Also associated with increased risk of suicide attempts and **REDUCED RESPONSIVENESS TO ANTIDEPRESSANTS**
- Why lower response? Because SSRIs essentially recycle serotonin, and you can't recycle or conserve something you don't have.

Clinical Significance HTR1A:

High-Risk Depression and Anxiety
Reduced responsiveness to antidepressants

Depression Pathway

Search Report...

Risk SNPs

SNP ID / Gene / Minor Allele	Patient Results / Prevalence	Variant	Key Point	Additional Information
rs6295 *HTR1A* G	CG 28.8%	1	5-Hydroxytryptamine Receptor 1A ***(lower serotonin signaling)*** ***Individuals with this SNP over downregulate the production and release of serotonin. This results in lower serotonin in various regions of the brain, which is associated with depression.***	Expand All Clinicial Significance Potential Interventions Gene Function / Summary Deeper Dive

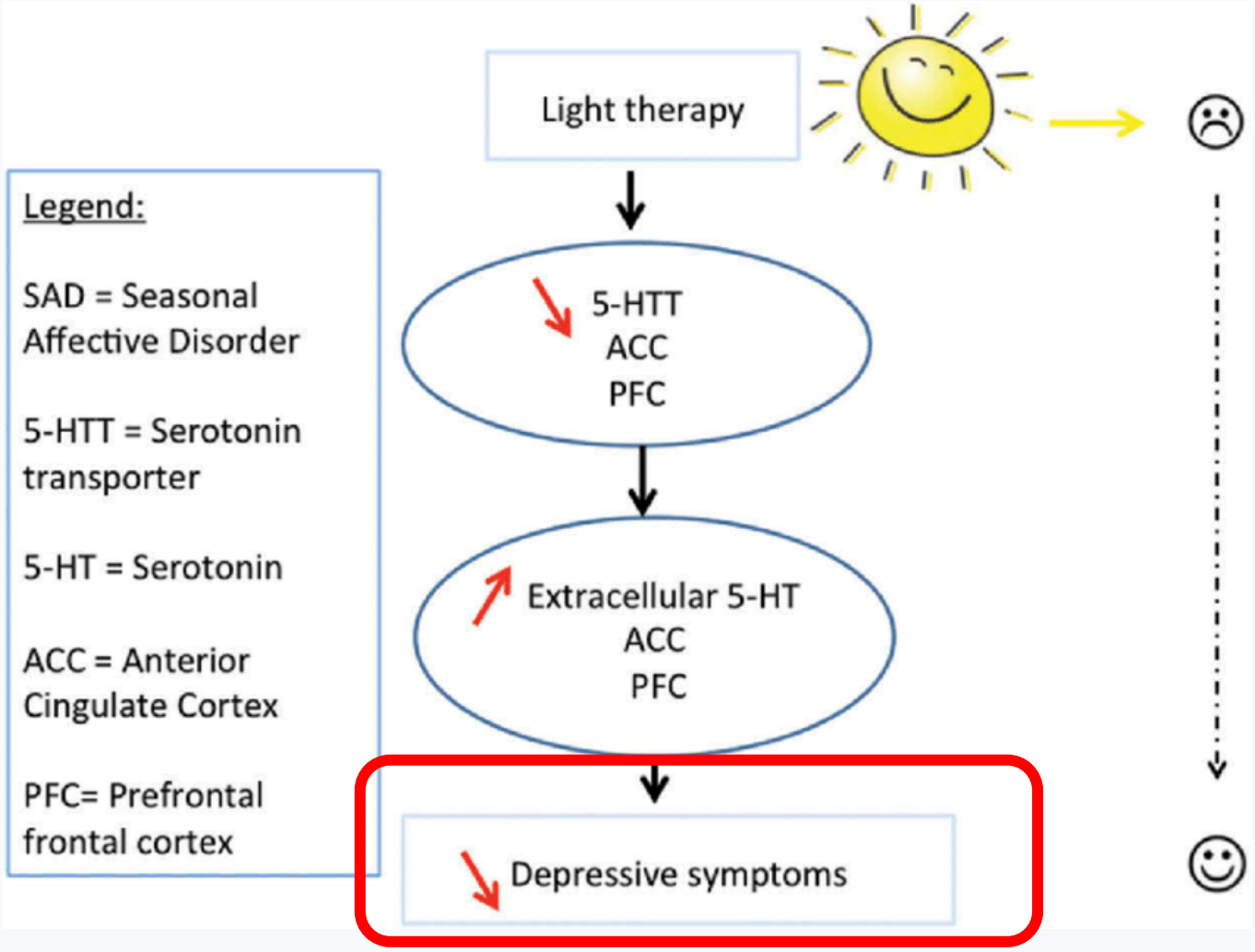
Clinical Significance: HTR1A

- Minor allele "G" associated with:
  - Comorbid generalized anxiety disorder and major depression (OR = 2.82) [18].
  - Increased risks of suicidal attempts, depression, and reduced responsiveness to antidepressants [20].
- Subjects carrying the GG genotype showed:
  - Significantly higher impulsiveness scores compared to GC or CC [21].

You can't recycle what you haven't produced. Since antidepressants recycle serotonin (and NE sometimes), they are less effective with this variant.

Addressing HTRA1 Variant:
10,000 Lux Light Therapy Decreases that Overactive Serotonin Transporter Binding in a Way that Raises Serotonergic Tone

There is a link between light exposure, serotonin binding and available extracellular serotonin levels.



Maruani, Julia, et al. 2018
Harrison, SJ et. al. 2015

Potential Interventions for HTR1A

Maximize the synthesis of serotonin as many ways as you can:

- 10,000 Lux light therapy
- Saffron
- SAMe
- Exercise

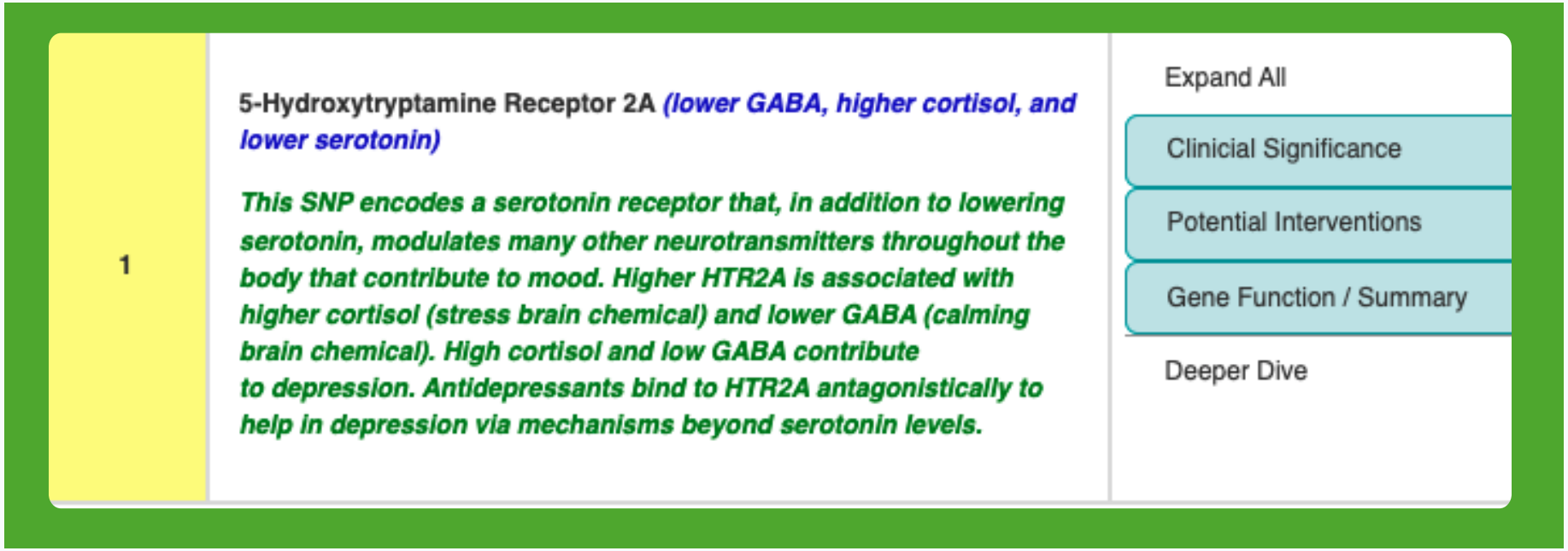
You can still use SSRIs and SNRIs, but they are less likely to be enough by themselves to get people into remission with this variant.

Cathy also had **HTRA2** serotonin receptor variant

Risk **SNP**	Gene **Risk allele**	Patient **Allele**	Variant (0, 1, 2)	Notes
rs79…	HTR1A G 28.9%	GC	1	5-Hydroxytryptamine Receptor 1A (lower serotonin signaling): • Even one copy of this gene variant is associated with 2.8 x the risk of depression and anxiety • Associated with lower response to antidepressants. Potential Interventions: 5-HTP extended release, SAMe, Saffron, exercise, bright light
rs62..	HTR2A A 40.9%	AG	1	5-Hydroxytryptamine Receptor 2A (lower GABA, higher cortisol, and lower serotonin) Higher HTR2A is associated with higher cortisol and lower GABA, which contributes to depression. Potential interventions: Increased response to citalopram and potentially other SSRIs. L-theanine and adaptogens like Magnolia officinalis, ashwagandha and rhodiola to lower cortisol may also be of benefit.
rs62,,	BDNF T 31.1%	TC	1	BDNF: Brain Derived Neurotrophic Factor (lower BDNF) This SNP is associated with lower conversion of proBDNF to the mature form • CT associated with 1.67 x risk depression • TT associated with 2.58 x risk of depression Potential Interventions: intense exercise, green coffee bean extract, hericeum erinaceus, high butyrate diet. SEE HANDOUT for other BNDF interventions.

HTR2A serotonin receptor variant

- This is a serotonin receptor that modulates not only serotonin levels but also affects cortisol levels and GABA levels
- Variant associated with higher HTR2A activity.
- SSRIs and SNRIs and atypicals bind to HTR2A antagonistically thus this variant is associated with BETTER response to these antidepressants.
- *Antidepressants (SSRIs, SNRIs and Atypicals) bind to HTR2A antagonistically and can help with this SNP in a mechanism not directly related to increasing serotonin.* ***That is why this SNP shows up in pharmacogenomic reports!***



Responding to **HTR2A** is a lot about Lowering Cortisol

- Medication-wise, SSRIs and SNRIs can help. This variant is associated with better response to SSRIs
- L-theanine can help increase GABA
- Ashwagandha and magnolia can help lower cortisol

This type of information is in Clinical Decision Tool Reports

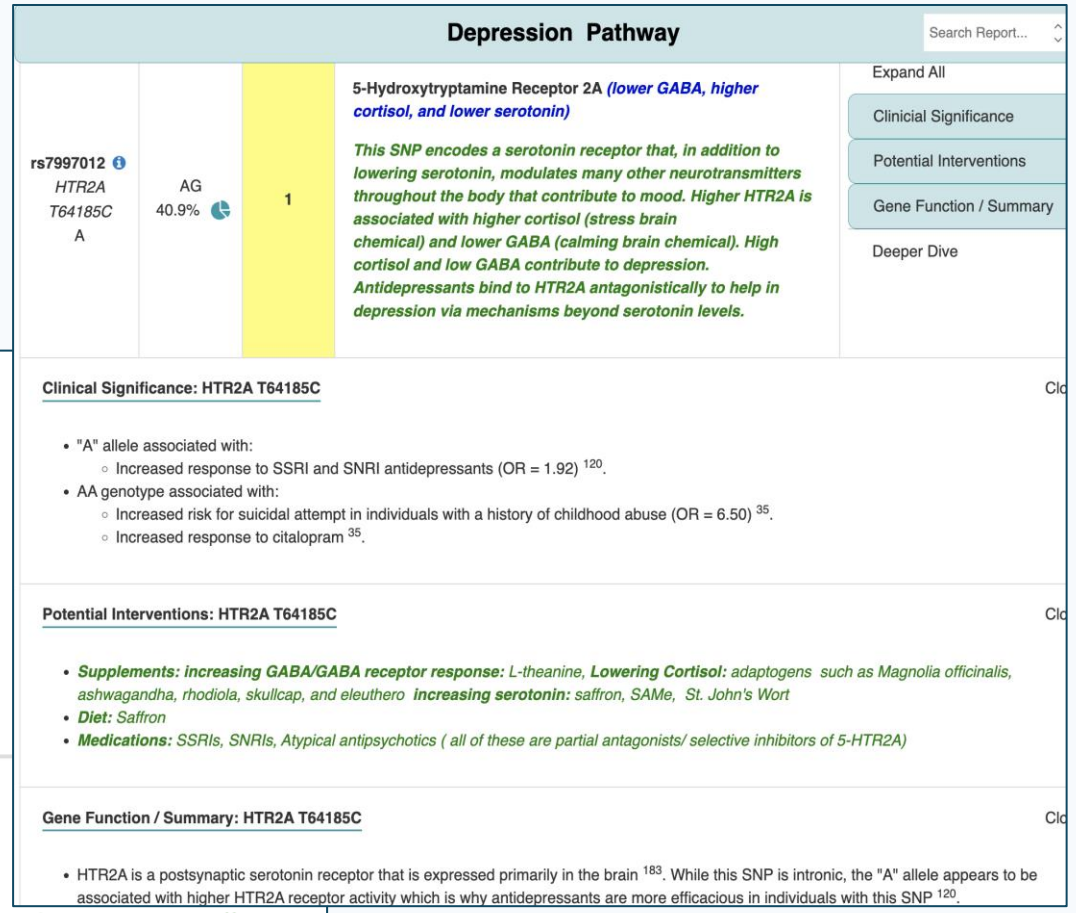
Other Potential Interventions are aimed at Increasing GABA and Decreasing Cortisol

This SNP is also part of the early adverse events story..

- "A" allele associated with:
  - Increased response to SSRI and SNRI antidepressants (OR = 1.92) [120].
- AA genotype associated with:
  - Increased risk for suicidal attempt in individuals with a history of childhood abuse (OR = 6.50) [35].
  - Increased response to citalopram [35].

Potential Interventions: HTR2A T64185C

- ***Supplements: increasing GABA/GABA receptor response:*** *L-theanine,* ***Lowering Cortisol:*** *adaptogens such as Magnolia officinalis, ashwagandha, rhodiola, skullcap, and eleuthero* ***increasing serotonin:*** *saffron, SAMe, St. John's Wort*
- ***Diet:*** *Saffron*
- ***Medications:*** *SSRIs, SNRIs, Atypical antipsychotics (all of these are partial antagonists/ selective inhibitors of 5-HTR2A)*



Other contributing factors…

Risk **SNP**	Gene **Risk allele**	Patient **Allele**	Variant (0, 1, 2)	Odds Ratio	Notes
rs42…	SLC6A15 A 23%	CC	2	2.8	Solute carrier for neutral amino acids (higher cortisol, amino acid driven) • Even one copy of this gene variant is associated with 2.8 x the risk of depression and anxiety • Associated with lower response to antidepressants. Potential Interventions: 5-HTP extended release, SAMe, Saffron, exercise, bright light
Rs 10..	MTHFR C677T A 12.5%	AA	2	1.2	MTHFR: Methylenetetrahydrofolate Reductase (lower neurotransmitter synthesis). Needed to make serotonin, norephinephrine and dopamine and to keep homocysteine under control. AG: Associated with 1.2 x risk depression AA: Associated with 1.4 x risk depression Potential Interventions: Methylfolate with riboflavin (since variant is in riboflavin binding site). B12 (needed for methylfolate to remove homocysteine)
Rs23,,	IL6 44.7%	TG	1	1.8	IL6: Increases IL6 mediated inflammation (high IL6 inflammation) • IL6 crosses the BBB and increases risk of depression • Can increase risk of vascular dementia in combination with MTHFR Potential Interventions: Curcumin, Quercetin, Sulforaphane

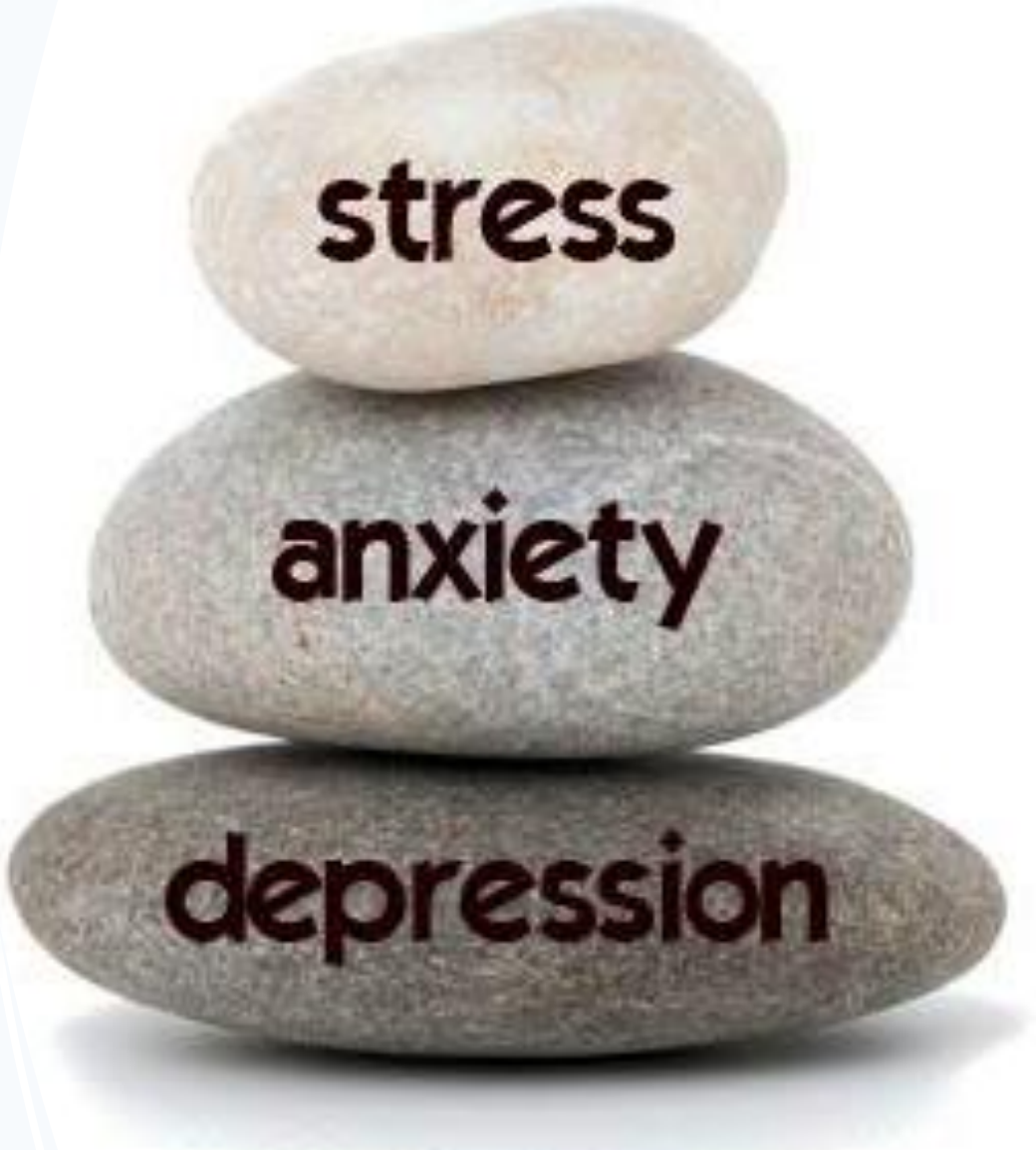
SLC6A15: Cathy had 2 copies of another solute carrier SNP associated with higher cortisol as well

- This gene variant increases ACTH and cortisol secretion
- In addition to depression, it has been associated with problems with sustained attention and memory.

High cortisol is one underlying root cause to depression

- This gene variant increases **ACTH and cortisol secretion**

- There are quite a few SNPs that cause higher cortisol associated with depression.



Randomized Controlled Trial > J Affect Disord. 2023 Jul 15:333:38-43.
doi: 10.1016/j.jad.2023.04.029. Epub 2023 Apr 19.

l-theanine adjunct to sertraline for major depressive disorder: A randomized, double-blind, placebo-controlled clinical trial

Ahmad Shamabadi [1], Farnaz Kafi [1], Melika Arab Bafrani [1], Hassan Asadigandomani [1], Fatemeh A Basti [2], Shahin Akhondzadeh [3]

Affiliations + expand

PMID: 37084960 DOI: 10.1016/j.jad.2023.04.029

Abstract

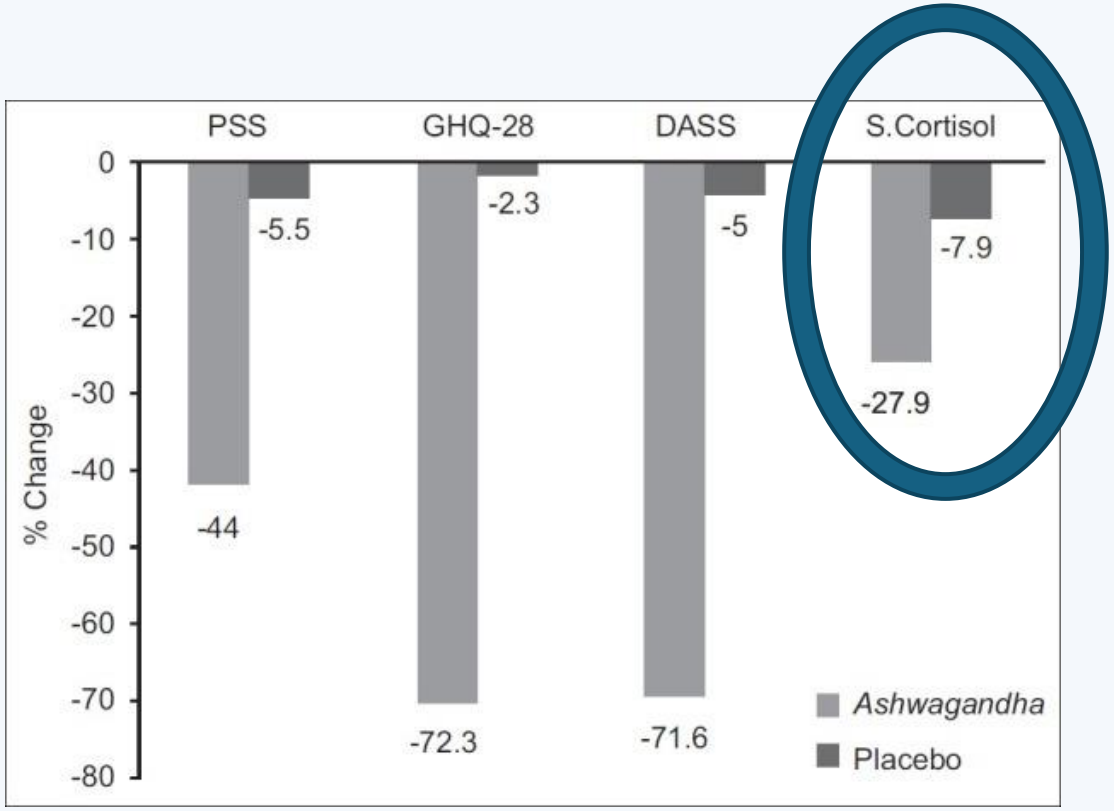
Background: Unsatisfactory responses to major depressive disorder (MDD) therapeutics available necessitated up-to-date treatment approaches. This study sought to investigate the efficacy and tolerability of adjunctive l-theanine, a green tea constituent with neuropsychotropic effects, for MDD.

L-Theanine was added to Cathy's regimen to Increase GABA Production for **HTR2A**

- Small study of patients with depression not in remission (60% of patients in the study were on anti-depressants):
  - 250 mg L-theanine daily given
  - Medications not changed
  - 46.2% of patients by 8 weeks were responders (50% or more reduction of HAM-D) with full remission (HAM-D of less than 4)
- L-theanine upregulates GABA receptors

Ashwagandha has been shown to effectively reduce cortisol levels.

There are no prescription drugs that lower cortisol and help depression but there are lots of great supplement options and natural options



Indian J Psychol Med. 2012 Jul;34(3):255-62. doi: 10.4103/0253-7176.106022.

A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults

K Chandrasekhar [1], Jyoti Kapoor, Sridhar Anishetty

Affiliations + expand

PMID: 23439798 PMCID: PMC3573577 DOI: 10.4103/0253-7176.106022

Abstract

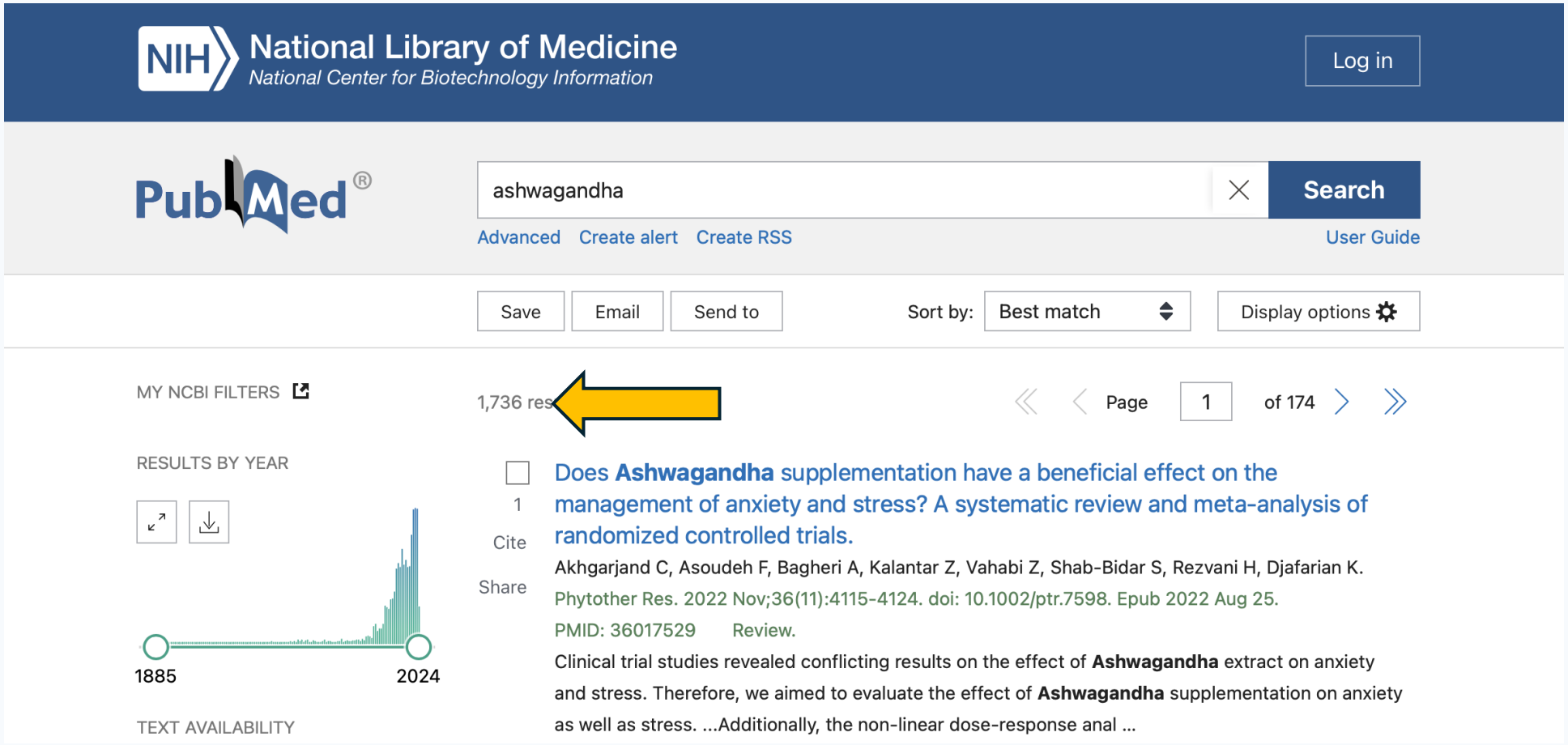
Context: Stress is a state of mental or emotional strain or tension, which can lead to underperformance and adverse clinical conditions. Adaptogens are herbs that help in combating stress. Ayurvedic classical texts, animal studies and clinical studies describe Ashwagandha as a safe and effective adaptogen.

Conclusion Ashwagandha study

Results: The treatment group that was given the high-concentration full-spectrum Ashwagandha root extract exhibited a significant reduction ($P<0.0001$) in scores on all the stress-assessment scales on Day 60, relative to the placebo group. Serum cortisol levels were substantially reduced ($P=0.0006$) in the Ashwagandha group relative to the placebo group. The adverse effects were mild in nature and were comparable in both groups. No serious adverse events were reported.

Conclusion: The findings of this study suggest that a high-concentration full-spectrum Ashwagandha root extract safely and effectively improves an individual's resistance towards stress and thereby improves self-assessed quality of life.

PubMed: Studies on Ashwagandha



BDNF: Another Contributing Factor for Cathy

rs1491850 *BDNF* C	CC 17.7%	2	**Brain-Derived Neurotrophic Factor** ***(serotonin antidepressant response)*** ***Brain-derived neurotrophic factor (BDNF) is a growth factor, kind of like fertilizer for the brain. This SNP is part of a group of SNPs that convey a better ability to respond to serotonin antidepressants. This is a more minor BDNF SNP.***	Collapse All Clinical Significance Potential Interventions Gene Function / Summary

Clinical Significance: BDNF Close ✖

- C allele has been associated with **an increased rate of left hippocampal atrophy, and increased risk of Alzheimer-related depression** [2].
- C allele is part of a haplotype (with T of rs6265) that conveys better ability to respond to SSRIs for depression [70].

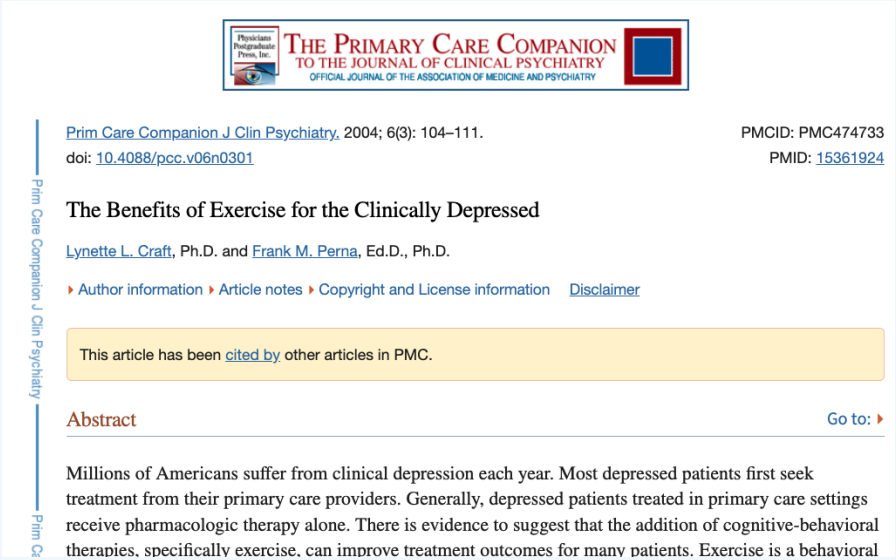
Addressing this Variant: **Exercise**

Exercise is the most economical way to boost BDNF production

Over 27,000 articles on exercise and depression

Cathy had a **BDNF SNP** Associated with 67% higher risk of depression

- Encouraged to exercise so could better convert proBDNF to BDNF
- ProBDNF is ”synaptoclastic” and triggers neurite retraction or loss
- Mature BDNF stimulates neurite growth and elongation



THE PRIMARY CARE COMPANION TO THE JOURNAL OF CLINICAL PSYCHIATRY
OFFICIAL JOURNAL OF THE ASSOCIATION OF MEDICINE AND PSYCHIATRY

Prim Care Companion J Clin Psychiatry. 2004; 6(3): 104–111.
doi: 10.4088/pcc.v06n0301
PMCID: PMC474733
PMID: 15361924

The Benefits of Exercise for the Clinically Depressed

Lynette L. Craft, Ph.D. and Frank M. Perna, Ed.D., Ph.D.

Abstract

Millions of Americans suffer from clinical depression each year. Most depressed patients first seek treatment from their primary care providers. Generally, depressed patients treated in primary care settings receive pharmacologic therapy alone. There is evidence to suggest that the addition of cognitive-behavioral therapies, specifically exercise, can improve treatment outcomes for many patients. Exercise is a behavioral

MINI REVIEW article
Front. Neurosci., 14 November 2018
Sec. Neuroenergetics, Nutrition and Brain Health
https://doi.org/10.3389/fnins.2018.00839
This article is part of the Research Topic
Nutrients, Neurotransmitters and Brain Energetics
View all 30 Articles

The Impact of High-Intensity Interval Training on Brain Derived Neurotrophic Factor in Brain: A Mini-Review

Alberto Jiménez-Maldonado[1*], Iván Rentería[1], Patricia C. García-Suárez[1], José Moncada-Jiménez[2] and Luiz Fernando Freire-Royes[3]

[1] Facultad de Deportes, Universidad Autónoma de Baja California, Ensenada, Mexico
[2] Human Movement Sciences Research Center, University of Costa Rica, San José, Costa Rica
[3] Laboratório de Bioquímica do Exercício, Universidade Federal de Santa Maria, Santa Maria, Brazil

The brain-derived neurotrophic factor (BDNF) is a protein mainly synthetized in the neurons. Early evidence showed that BDNF participates in cognitive processes as measured at the hippocampus. This neurotrophin is as a reliable marker of brain function; moreover, recent studies have demonstrated that BDNF participates in physiological processes such as glucose homeostasis and lipid metabolism. The BDNF has been also studied using the exercise paradigm to determine its response to different exercise modalities; therefore, BDNF is considered a new member of the exercise-related molecules. The high-intensity interval training (HIIT) is an exercise protocol characterized by low work volume performed at

Additional Ways to Increase BDNF

Diet:

- ***Butyrate-producing foods:*** *Raise BDNF levels* [1]
- ***High fiber foods:*** *Raise BDNF levels* [5]
- ***Prebiotics:*** *Raise BDNF levels* [10]
- ***Blueberries:*** *Raise BDNF levels* [63].

Lifestyle:

- ***Moderate to intense exercise:*** *Converts pro-BDNF to mature form (best evidence)* [10].

Medications:

- ***SSRIs:*** *Raise BDNF levels* [9]

But also, other contributing factors…

Risk **SNP**	Gene **Risk allele**	Patient **Allele**	Variant (0, 1, 2)	Odds Ratio	Notes
rs42…	SLC6A15 A 23%	CC	2	2.8	Solute carrier for neutral amino acids (higher cortisol, amino acid driven) • Even one copy of this gene variant is associated with 2.8 x the risk of depression and anxiety • Associated with lower response to antidepressants. Potential Interventions: 5-HTP extended release, SAMe, Saffron, exercise, bright light
Rs 10..	MTHFR C677T A 12.5%	AA	2	1.2	MTHFR: Methylenetetrahydrofolate Reductase (lower neurotransmitter synthesis). Needed to make serotonin, norephinephrine and dopamine and to keep homocysteine under control. AG: Associated with 1.2 x risk depression AA: Associated with 1.4 x risk depression Potential Interventions: Methylfolate with riboflavin (since variant is in riboflavin binding site). B12 (needed for methylfolate to remove homocysteine)
Rs23,,	IL6 44.7%	TG	1	1.8	IL6: Increases IL6 mediated inflammation (high IL6 inflammation) • IL6 crosses the BBB and increases risk of depression • Can increase risk of vascular dementia in combination with MTHFR Potential Interventions: Curcumin, Quercetin, Sulforaphane

Cathy also had 2 Copies of the famous MTHFR C677T

This is one of the best-known genes in psychiatry.

rs1801133 *MTHFR* *C677T* A	AA 12.5%	2	Methylenetetrahydrofolate Reductase ***(lower neurotransmitter synthesis)*** ***MTHFR is one of the more famous SNPs. It is needed to make the brain chemicals of serotonin (mood), norepinephrine (attention), dopamine (pleasure), melatonin (sleep) and acetylcholine (memory). It is also responsible for recycling homocysteine back to methionine (which is the main methyl donor for SAMe). Methylation is an important reaction in our body that helps regulate (turn off) genes.***	Expand All Clinicial Significance Potential Interventions Gene Function / Summary Deeper Dive

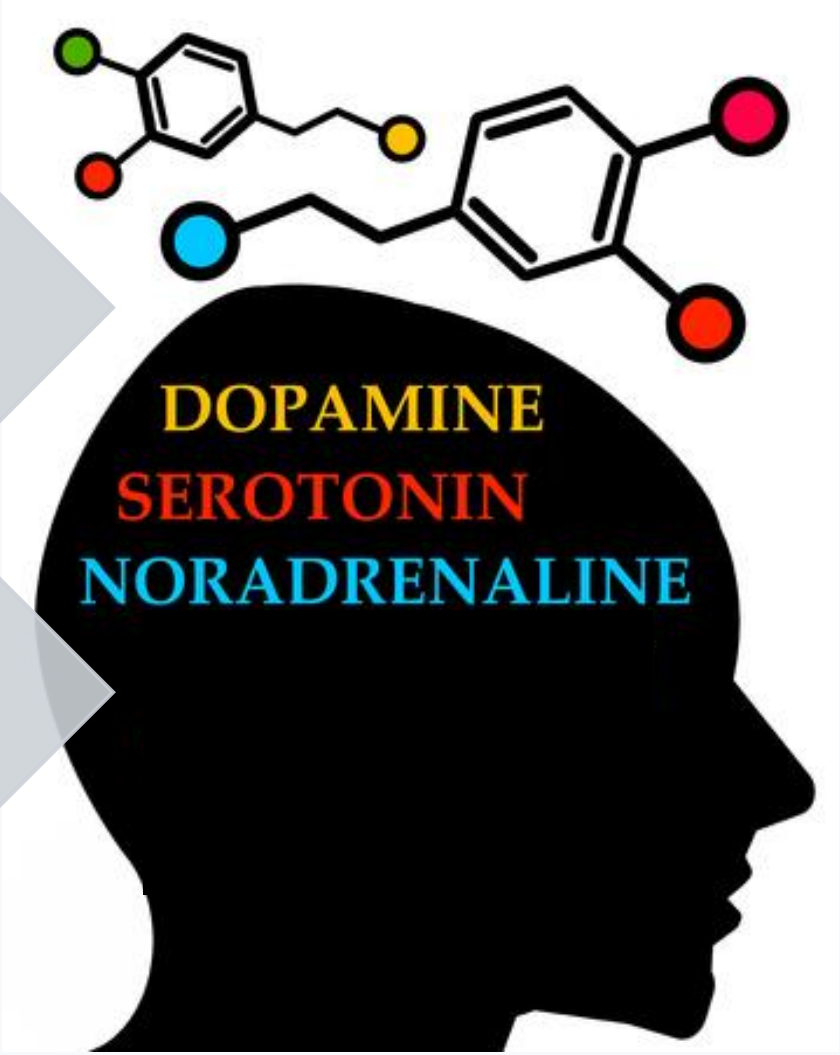
Folic Acid Doesn't Cross the BBB. Methylfolate is Needed to Make Neurotransmitters

Methylfolate + BH4 +Tryptophan

- Serotonin
- Melatonin

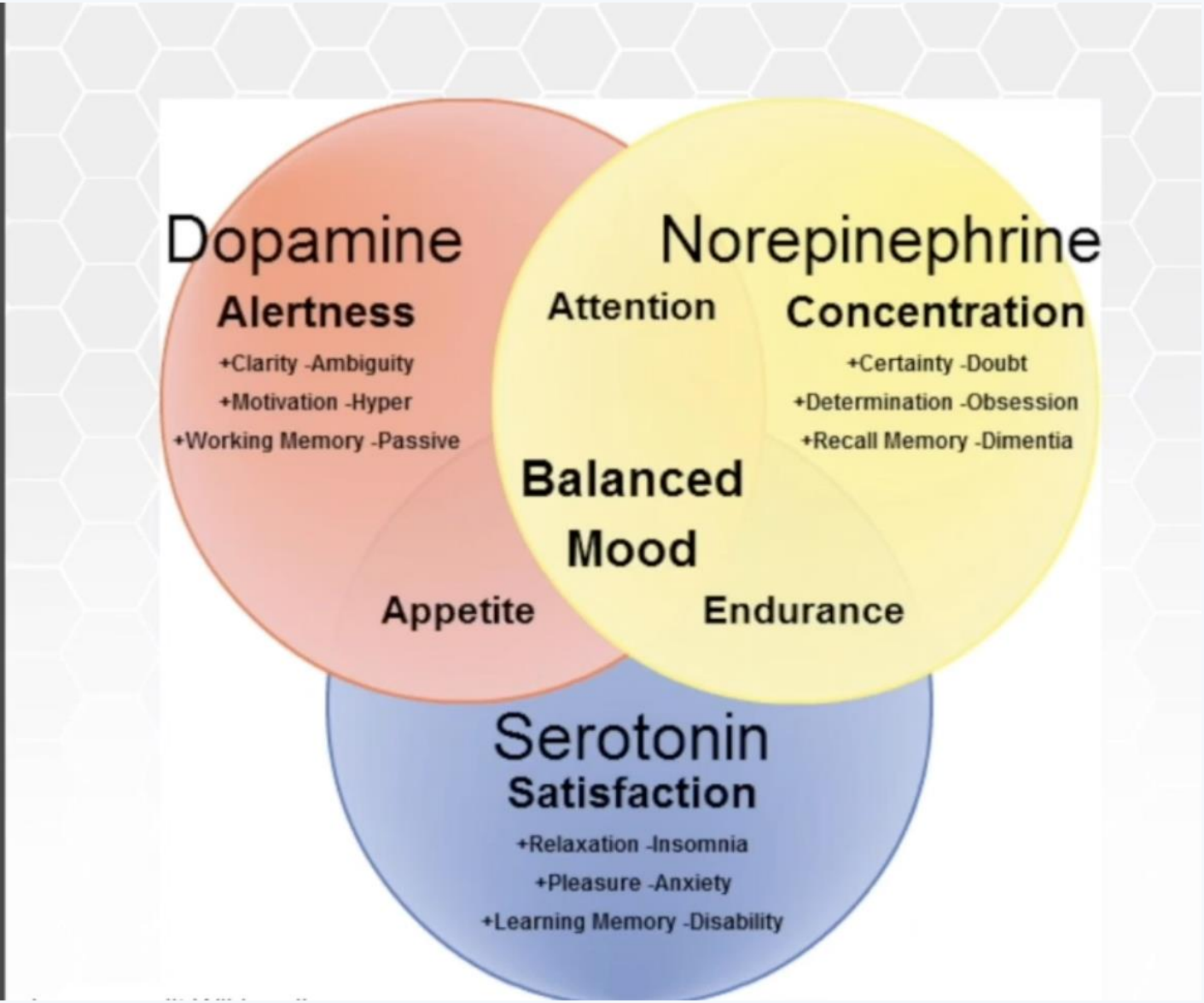
Methylfolate +BH4 +Tyrosine

- Dopamine
- Norepinephrine



MTHFR C677T and Alzheimer's

- Each copy of the minor allele corresponds to about 35% lower production of essential nutrient methylfolate.
- Methylfolate (MTHFR) is necessary for synthesis of:
  - Acetylcholine from Phosphatidylcholine
  - Norepinephrine & Dopamine from Tyrosine
  - Serotonin & Melatonin

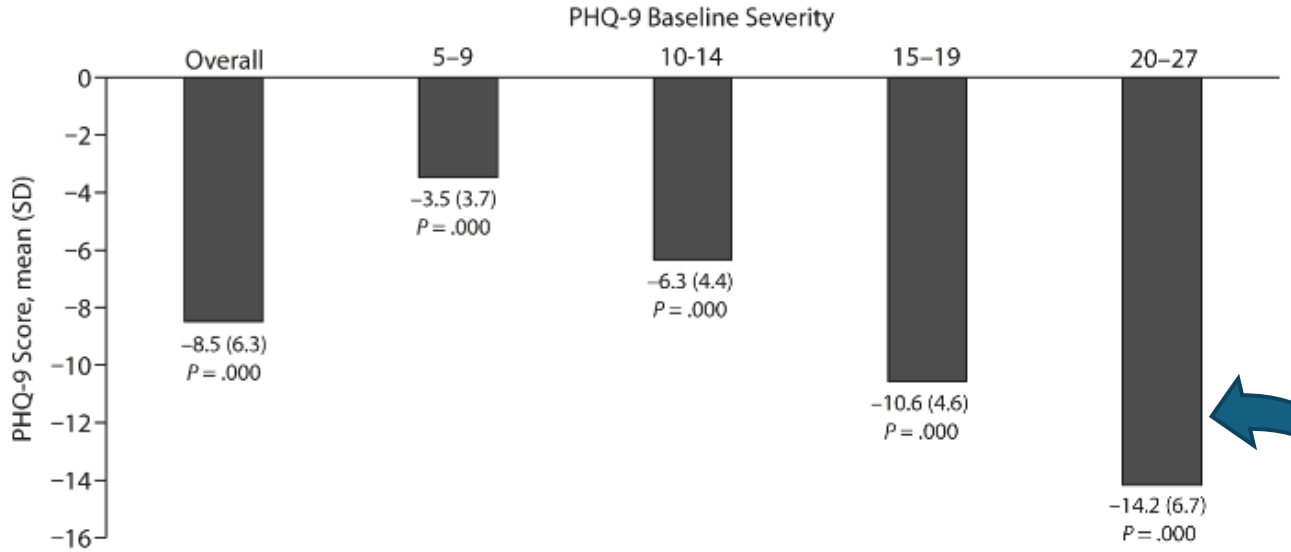


Methylfolate Improved Outcomes in People Already on Antidepressants –

Makes Sense Because They Were Now Better Able to Synthesize Serotonin

Figure 1. Change in Depression Severity Score

A. Mean Change in PHQ-9 Score by Baseline Severity



502 patients were on antidepressants.
52 got L-methylfolate 7.5-15 mg alone

Notice: People who still had severe depression had an average drop in PHQ9 of 14 points

rs1801133 *MTHFR* *C677T* A	AA 12.5%	2	**Methylenetetrahydrofolate Reductase** ***(lower neurotransmitter synthesis)*** ***MTHFR is one of the more famous SNPs. It is needed to make the brain chemicals of serotonin (mood), norepinephrine (attention), dopamine (pleasure), melatonin (sleep) and acetylcholine (memory). It is also responsible for recycling homocysteine back to methionine (which is the main methyl donor for SAMe). Methylation is an important reaction in our body that helps regulate (turn off) genes.***

Expand All

Clinicial Significance

Potential Interventions

Gene Function / Summary

Deeper Dive

Clinical Significance: MTHFR C677T Close ×

- The variant allele (A) has been associated with increased risk of:
  - Depression [142, 143].
    - AG (OR = 1.20 in large meta-analysis) [142].
    - AA (OR = 1.37 in large meta-analysis) [142].
  - Cognitive impairment [143].
  - Spina bifida [143].
  - Age-related hearing loss in males (OR = 2.2) [144].
  - Some types of cancer [143].
- Individuals with two variants (AA genotype) are associated with:
  - Lower plasma folate levels [145].
  - Elevated homocysteine levels [145].
  - Increased risk for male infertility [143].
  - Very high risk of age-related hearing loss in males (4.88x risk for AA) [144].

Did you know this variant is in the **riboflavin binding site** and will work better when combined with riboflavin?

You will notice that evidence-based intervention for MTHFR is more than just methyl folate.

Potential Interventions: MTHFR C677T Close ×

- ***Supplements:*** *Methylfolate (direct intervention), riboflavin (key as this variant is in riboflavin binding site), Vitamin B12 (necessary for methylfolate to remove homocysteine via methionine synthase), Choline. Vitamin C to reduce endothelial dysfunction from elevated homocysteine.*
- ***Diet:*** *Dietary intake of Vitamin B12, C, choline, folate, and riboflavin can be beneficial. See Handouts on these nutrient-containing foods in the Document Library.*

Remember Cathy's IBS-D, migraines and ADHD?

She was in the 7.1 % of the population at the highest risk of histamine intolerance, and 7.3% of population problems with CoQ10,

Gene Minor Allele	Patient Results Prevalence	Variant	Panel	SNP Key Point
AOC1 (ABP1) T	TT 7.1%	2	**Histamine Intolerance and Food Sensitivity**	Amine Oxidase Copper Containing 1 ***(histamine)*** ***This enzyme is needed for breaking down histamine from foods. Individuals with this SNP have increased risk for "histamine intolerance", which often manifests as GI symptoms.***
NQO1 A	AG 7.3%	1	**Environmental Toxins (Benzene)**	NAD(P)H Quinone Dehydrogenase 1 ***(smoke, pollution, benzene, superoxide, and various toxins)*** ***Individuals with this SNP have impaired ability to get rid of toxins, particularly environmental toxins such as benzene and smoke, due to decreased NQO1 enzyme activity. This SNP also makes it difficult to recycle CoQ10 and vitamin E to their active forms.***
HTR1B G	GG 7.7%	2	**Attention and Focus**	5-Hydroxytryptamine Receptor 1B ***(higher glutamate and dopamine, lower GABA via serotonin dysregulation)*** ***This SNP leads to more binding and activation of this receptor, which increases glutamate and dopamine, and lowers GABA. While this SNP is part of a serotonin receptor, it affects the regulation of these other brain chemicals. Variants have been associated with lower response to medications that increase serotonin such as Lexapro, Celexa, Prozac, and Zoloft.***
EPHX1 C	CC 9.1%	2	**Environmental Toxins (Benzene)**	Epoxide Hydrolase 1 ***(epoxides, benzene, pesticides, dyes, diesel exhaust, tobacco smoke, styrene)*** ***Individuals with this SNP have impaired ability to clear aromatic amines (pesticides, dyes, diesel exhaust, tobacco smoke, styrene). Lower ability to clear these aromatic amines can result in increased oxidative stress and a higher risk of environmentally-induced health conditions.***

Discoveries With A Genomic Clinical Decision Tool: Cathy

Refractory depression on high dose Zoloft and still PHQ-13

Gene variants discovered with one genomic swab:

HTR1A	HTR2A	SLC6A15	BDNF	MTHFR C677T	AOC1	NQO1

Case of Cathy

- Sertraline 50 mg (to regulate HTR2A)
- Happy Light 10,000 lux light to increase serotonin synthesis (especially in winter to regulate HTR1A)
- Homocysteine supreme – 2 daily (Vitamin B6 (5P5), methyl folate, Vitamin B12 and Riboflavin) for MTHFR
- Ashwagandha 500 mg qd (with extra if needed) (for SLC6A15)
- Regular exercise –(For BDNF)
- Ubiquinol (activated CoQ10) 100 mg (NQO1)
- DAO enzymes with high histamine foods hx of migraines (AOC1)

Cathy’s PHQ9 started out at 13 on her previous regiment.

Current PHQ9 Score: **0**

Added Bonuses for Cathy:

Migraines gone!

-Methyl folate with B vitamins has been shown to help with migraines

-Uncovered histamine intolerance

-Inability to recycle CoQ10 well was uncovered

A better understanding of herself.

Cathy nearly cried when she finally understood why she had struggled with treatment-resistant depression her whole life. She felt validated and no longer felt like it was her “fault” or a personality flaw.

Pharmacists are the perfect healthcare professionals for Root Cause Genomics

No one is better suited or have the knowledge base better than a pharmacist to take this approach

Image a time when you go to the doctor for a diagnosis but they don't write a prescription for medicine. The prescription is genomics and the pharmacist determines root cause and prescription plan

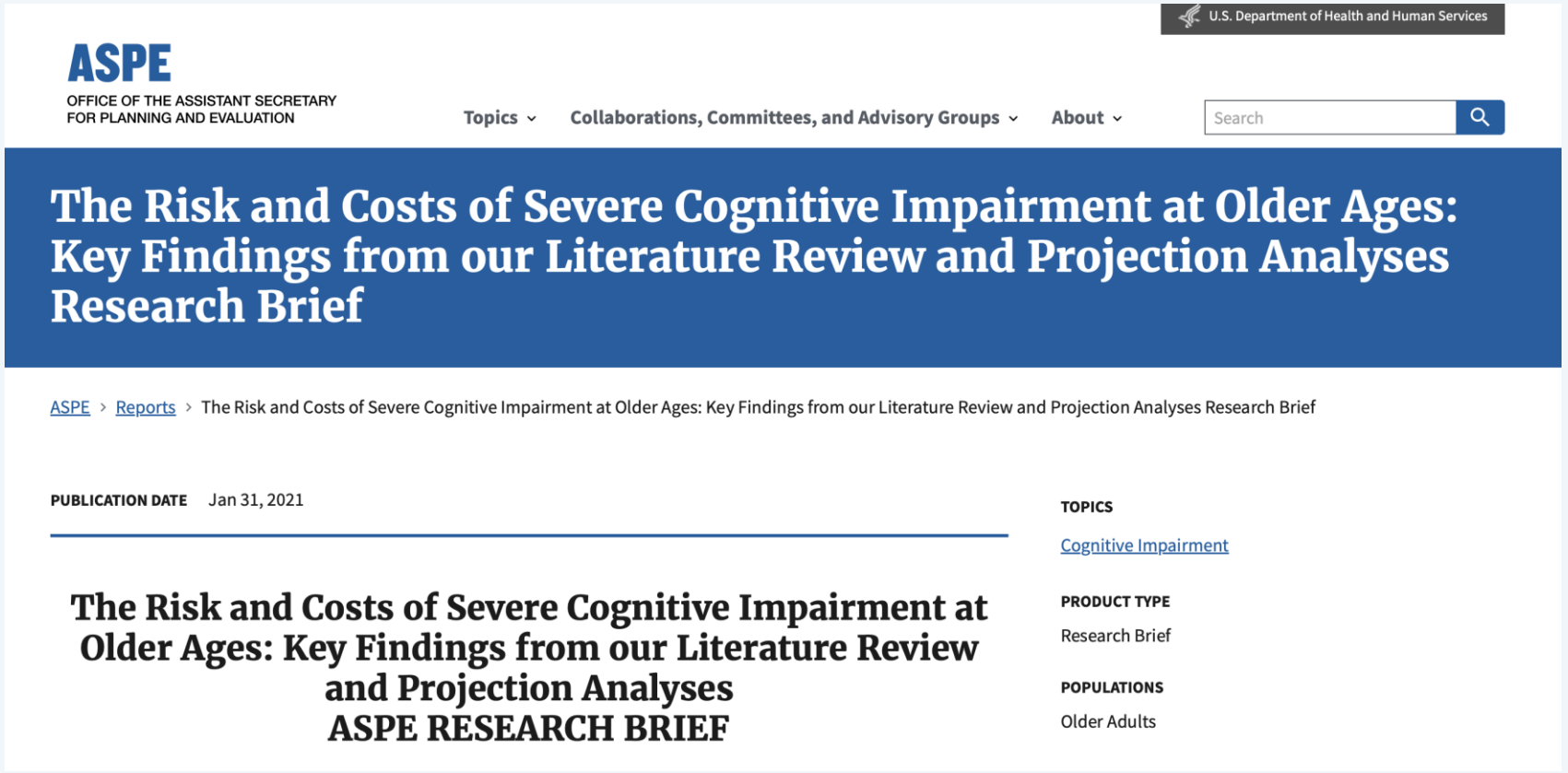
Medicine is changing at lightspeed. We as a profession are primed to insert ourselves in this position.

Most of us probably need this about now…

Welcome to Rocket Science Medicine!

Cognitive Genomics

- Prevention of cognitive decline
- Treatment and reversal of cognitive decline



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The Risk and Costs of Severe Cognitive Impairment at Older Ages: Key Findings from our Literature Review and Projection Analyses Research Brief

ASPE › Reports › The Risk and Costs of Severe Cognitive Impairment at Older Ages: Key Findings from our Literature Review and Projection Analyses Research Brief

PUBLICATION DATE Jan 31, 2021

The Risk and Costs of Severe Cognitive Impairment at Older Ages: Key Findings from our Literature Review and Projection Analyses
ASPE RESEARCH BRIEF

TOPICS
Cognitive Impairment

PRODUCT TYPE
Research Brief

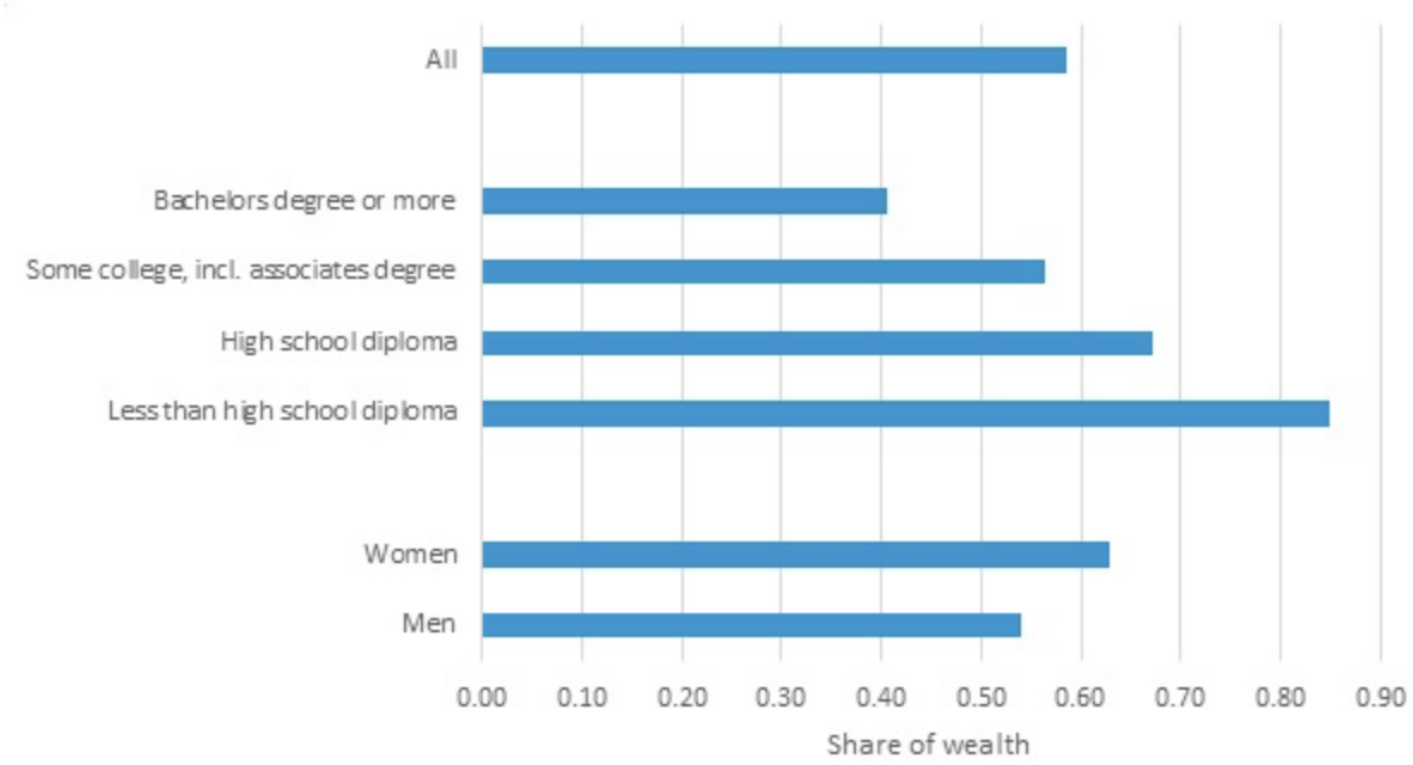
POPULATIONS
Older Adults

Cognitive Genomics: Why It Matters

- 31% of older adults born from 1955-1959 in the United States and who survive to 65 will become cognitively impaired.
- Health risks--like obesity and diabetes--have grown among older adults and could affect the future trajectory of cognitive impairment.
- Those lower in the income distribution can expect to use most or all of their wealth on care should they become impaired

Cognitive Genomics: Why It Matters

FIGURE 8. Projected Out-of-Pocket LTSS Spending from Age 65 while SCI as a Percentage of Financial Wealth 5 Years Before Death: DYNASIM 1955-1959 Birth Cohorts, by Gender and Education



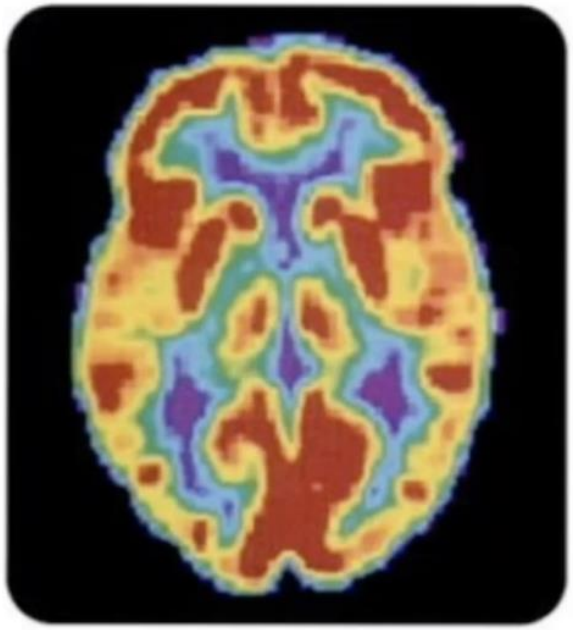
16,000,000 in US Affected by Cognitive Decline

What if there is a way to reverse this decline and help these individuals and their families?

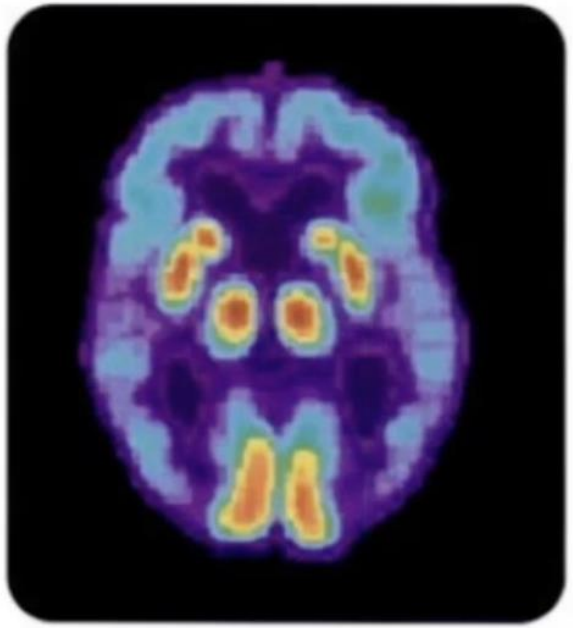
What if the memory problems could be prevented ?

Dr. Bredesen Divides His Cognition Patients into 6 Types:

- Type 1: “Inflammatory”
- Type 1.5: “Glycotoxic”
- Type 2: “Atrophic”
- Type 3: “Toxic”
- Type 4: “Vascular”
- Type 5: “Traumatic”



PET Scan of Normal Brain



PET Scan of Alzheimer's Disease Brain

Picture from: Apolipoprotein E ε4 is associated with disease-specific effects on brain atrophy in Alzheimer's disease and frontotemporal dementia Federica Agosta, et al. Proceedings of the National Academy of Sciences Feb 2009, 106 (6) 2018-2022; DOI:10.1073/pnas.0812697106

Some of the kinds of protein coding genes and regulatory genes related to brain function...

- Transporters for vitamins and minerals into the cells and across BBB
- Enzymes that process amyloid
- The growth factors that allow repair of nerves
- The cytokines that signal inflammation
- The neurotransmitters needed for memory and mood
- Hormone enzymes and activators
- The clean up molecules that remove toxins and waste from our body

Part1: A focus on Apo ε4

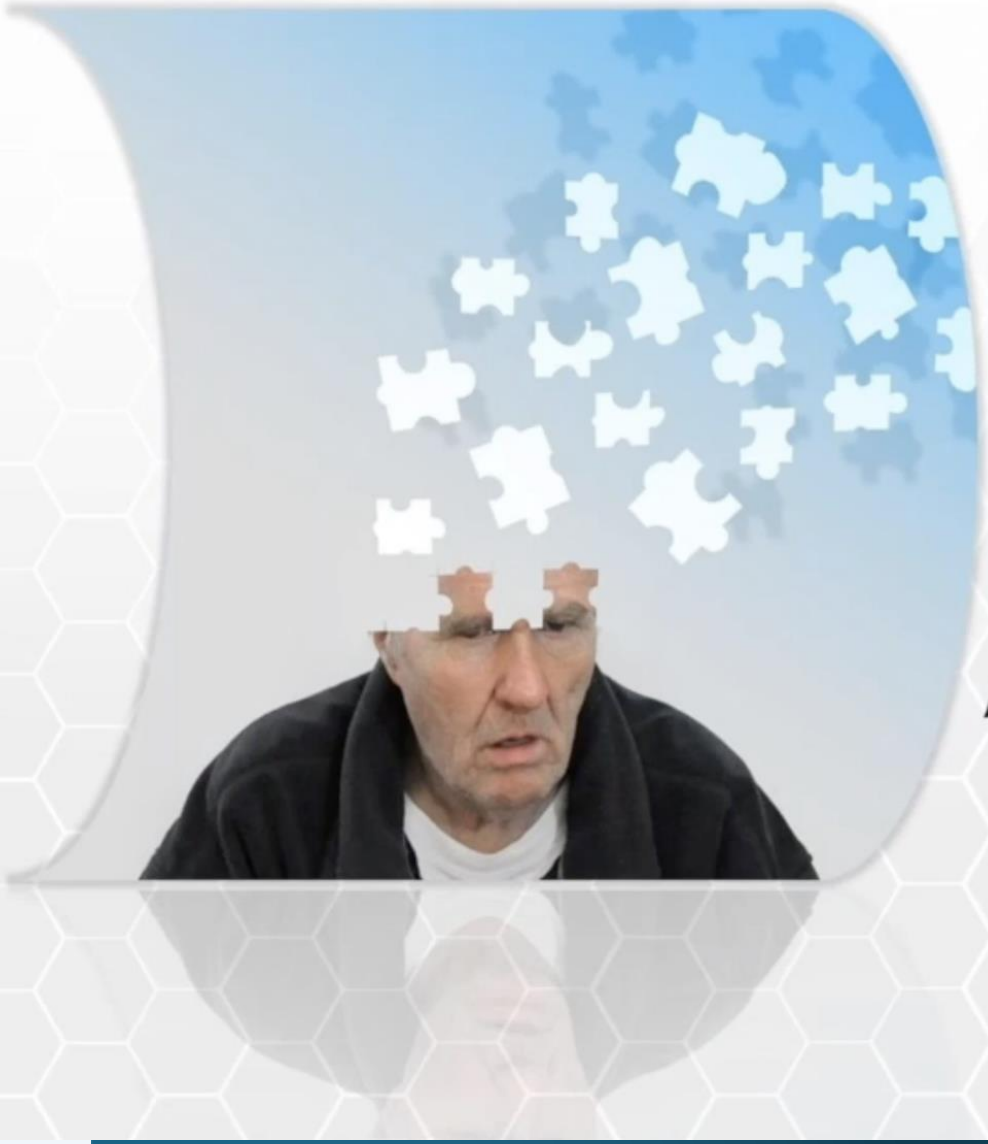
Review: The Science behind ApoE ε4

Understand: Genomic pathways that interact with ApoE ε4 and contribute to cognition.

APOE ε4: main "LOAD" risk factor

High magnitude of risk (OR 2-13 fold)

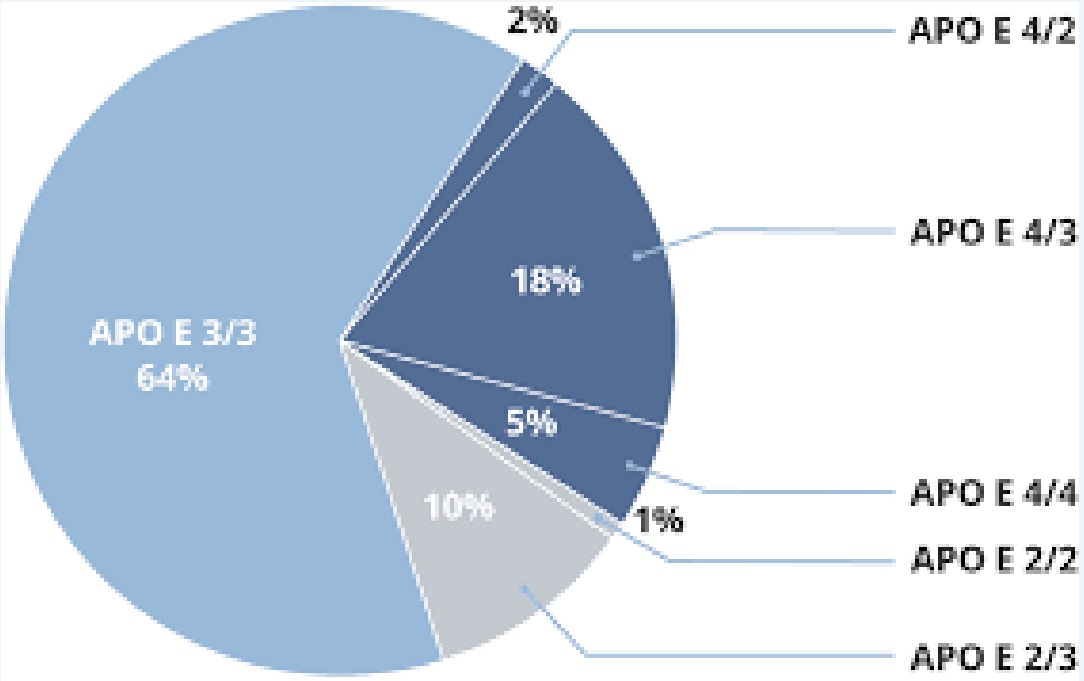
~ 16-20% prevalence



ApoE*ε4 allele - found in approximately 70% of individuals who develop Alzheimer's before age 80.

ApoE4 carriers account for approximately 65% of all AD cases.
(Studies range from 40-80%)

Understanding APOE Risks



ApoE is a lipoprotein that binds to 1700 different promoter regions

J Neurosci. 2016 Jan 20;36(3):685-700. doi: 10.1523/JNEUROSCI.3962-15.2016.

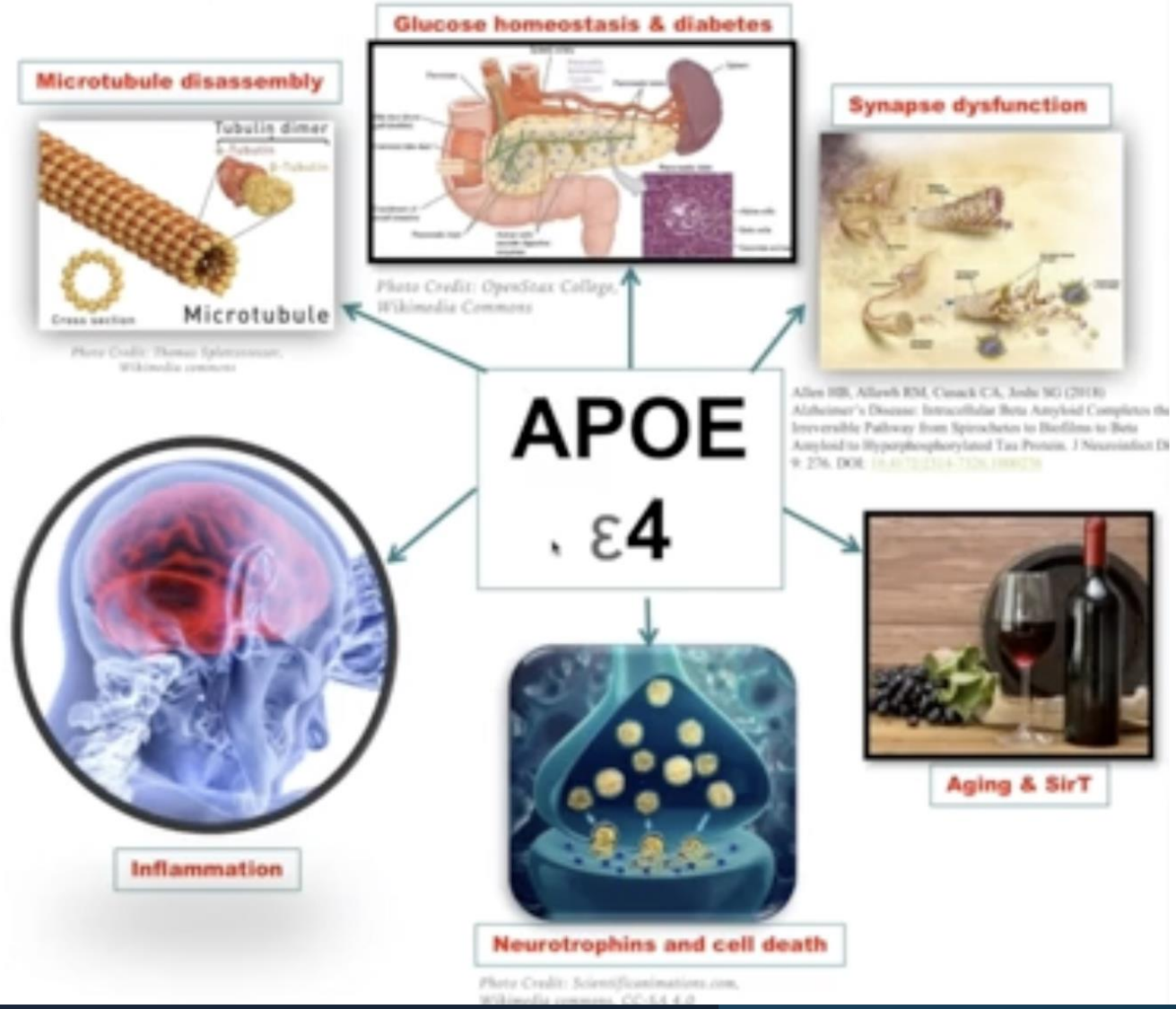
Direct Transcriptional Effects of Apolipoprotein E.

Theendakara V[1], Peters-Libeu CA[1], Spilman P[2], Poksay KS[1], Bredesen DE[3], Rao RV[4].

Author information

Abstract

A major unanswered question in biology and medicine is the mechanism by which the product of the apolipoprotein E ε4 allele, the lipid-binding protein apolipoprotein E4 (ApoE4), plays a pivotal role in processes as disparate as Alzheimer's disease (AD; in which it is the single most important genetic risk factor), atherosclerotic cardiovascular disease, Lewy body dementia, hominid evolution, and inflammation. Using a combination of neural cell lines, skin fibroblasts from AD patients, and ApoE targeted replacement mouse brains, we show in the present report that ApoE4 undergoes nuclear translocation, binds double-stranded DNA with high affinity (low nanomolar), and functions as a transcription factor. Using chromatin immunoprecipitation and high-throughput DNA sequencing, our results indicate that the ApoE4 DNA binding sites include ~1700 gene promoter regions. The genes associated with these promoters provide new insight into the mechanism by which AD risk is conferred by ApoE4, because they include genes associated with trophic support, programmed cell death, microtubule disassembly, synaptic function, aging, and insulin resistance, all processes that have been implicated in AD pathogenesis. Significance statement: This study shows for the first time that apolipoprotein E4 binds DNA with high affinity and that its binding sites include 1700 promoter regions that include genes associated with neurotrophins, programmed cell death, synaptic function, sirtuins and aging, and insulin resistance, all processes that have been implicated in Alzheimer's disease pathogenesis.



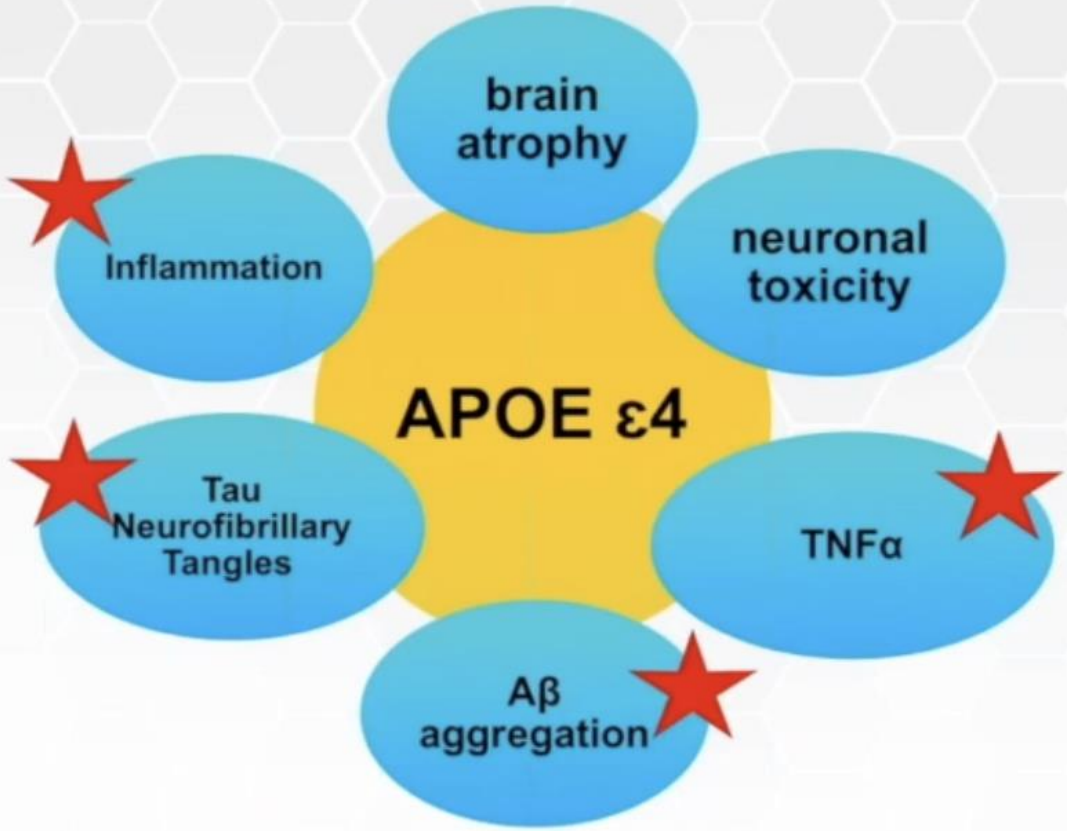
APOE ε4 HAS DIFFERENT SHAPE WHICH CHANGES FUNCTIONAL ABILITY

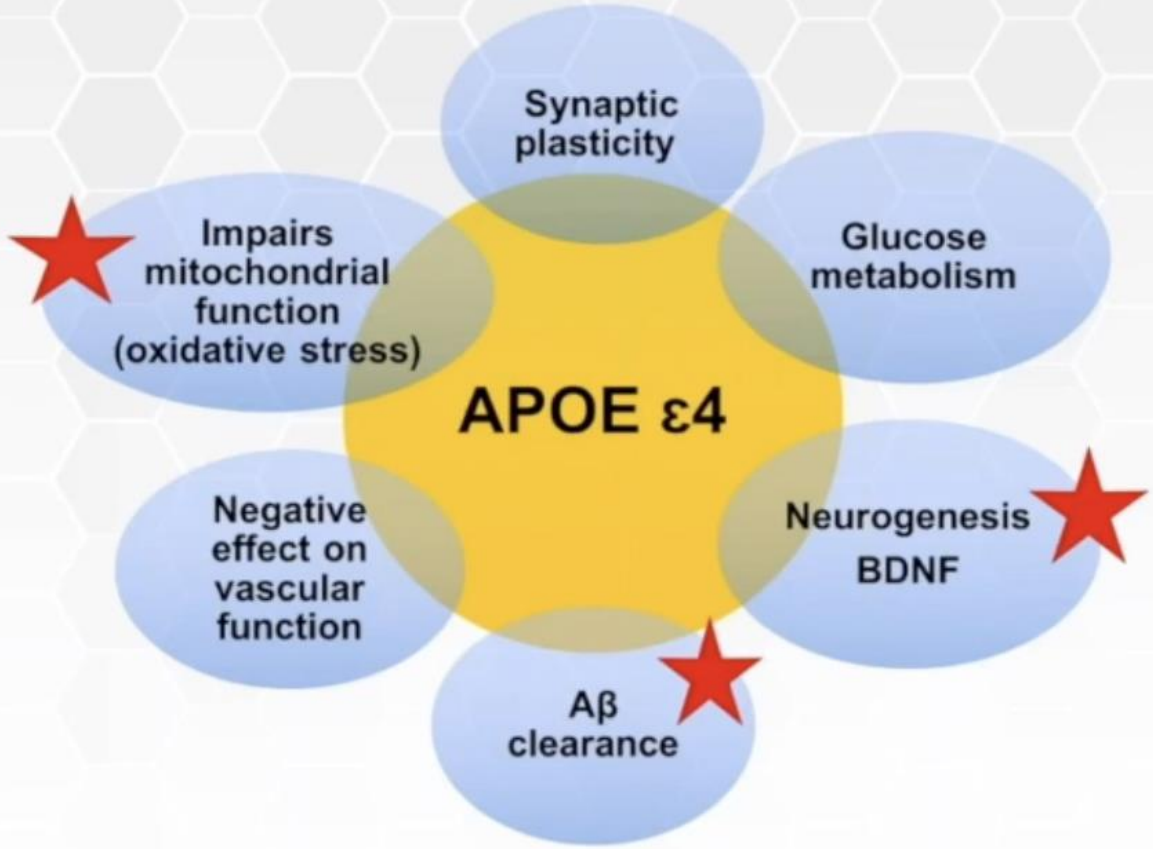
- **APOE*ε4 is associated with:**
  - Decreases the function of ApoE due to altered shape to molecule
  - Less of the ApoE molecule
  - Decreased ability to clear amyloid β
- **APOE*ε2 is associated with:**
  - Increased production of ApoE
  - Increased LDL and amyloid β clearance

Kwang-Min Kim and G. Tayhas R. Palmore (2017). Lipoproteins and Diseases of the Brain, Advances in Lipoprotein Research, Prof. Turgay Ishir (Ed.), InTech, DOI: 10.5772/67053. Available from: https://www.intechopen.com/books/advances-in-lipoprotein-research/lipoproteins-and-diseases-of-the-brain

What makes APOE4 Different?

APOE ε4 HAS MANY DIFFERENT EFFECTS





APOE ε4 increases above

APOE ε4 decreases above

APOE4: Contraindication

Leqembi Approval Likely to Drive Changes in APOE Testing Landscape

Sep 21, 2023 | Adam Bonislawski

August 2023 NEUROSCIENCES

LEQEMBI: WHAT PHYSICIANS NEED TO KNOW ABOUT THE NEW ALZHEIMER'S DRUG

Featuring: Ian M. Grant, MD

Dr. Grant says about one in five patients on Leqembi experience amyloid-related imaging abnormalities (ARIA), generally asymptomatic swelling or bleeding in the brain. But sometimes ARIA is accompanied by transient symptoms, such as headache, confusion and visual disturbance. Rarely, ARIA presents as life-threatening brain edema and bleeding.

Review > Adv Clin Exp Med. 2023 Sep;32(9):943-947. doi: 10.17219/acem/171379.

Lecanemab (Leqembi) is not the right drug for patients with Alzheimer's disease

Markku Kurkinen [1]

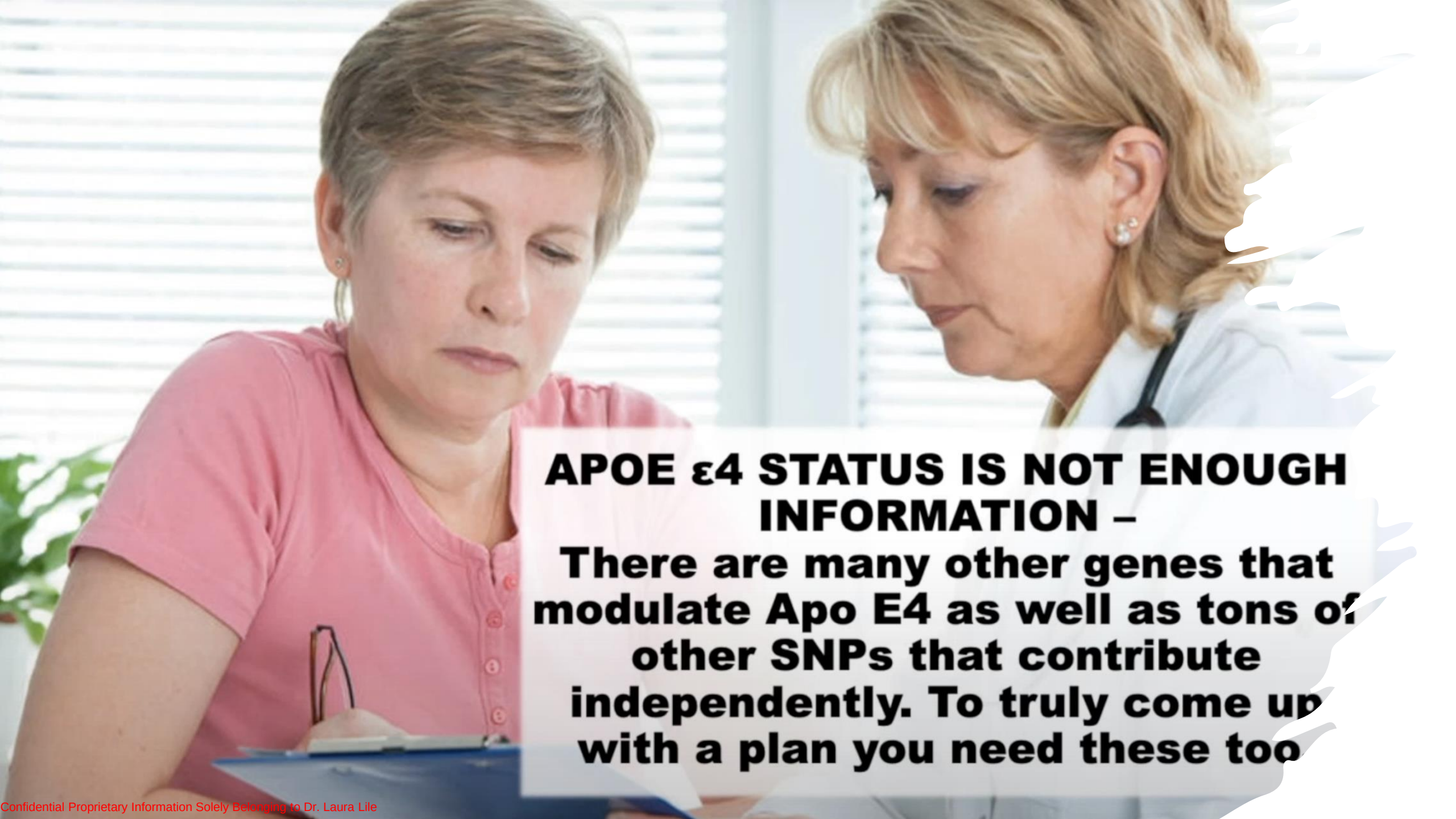
Affiliations + expand

PMID: 37676096 DOI: 10.17219/acem/171379

Free article

Abstract

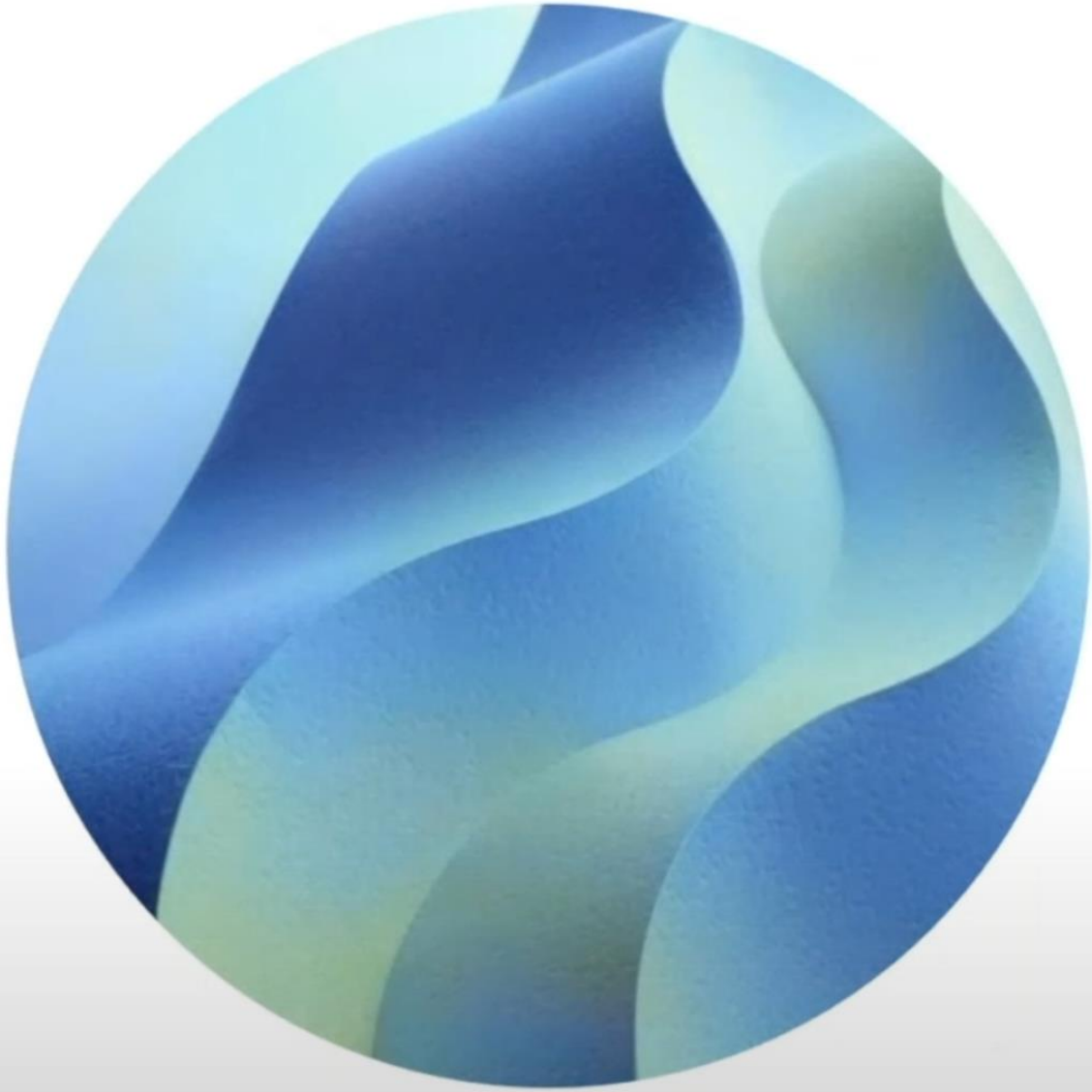
On July 6, 2023, the U.S. Food and Drug Administration (FDA) approved lecanemab (Leqembi) for the treatment of Alzheimer's dementia (AD) patients. In 2 clinical trials, lecanemab reduced amyloid in the brain and slowed cognitive decline. Here, I review in detail the clinical trial by van Dyck et al. (2023) entitled "Lecanemab in early Alzheimer's disease", published in The New England Journal of Medicine on January 5, 2023. In this 18-month trial, lecanemab did not slow cognitive decline in women. This is especially significant because women have a twofold increased risk of AD compared to men, that is, there are 2 times more women than men living with AD. Lecanemab did not slow cognitive decline in APOE4 carriers; rather, it enhanced the decline in study participants with 2 APOE4 genes. This is bad news for AD patients, 60-75% of whom carry at least 1 APOE4 gene. These negative results regarding lecanemab's therapeutic value make me wonder if the approval of lecanemab was the worst decision of the FDA up till now, after the approval of aducanumab on June 7, 2021.



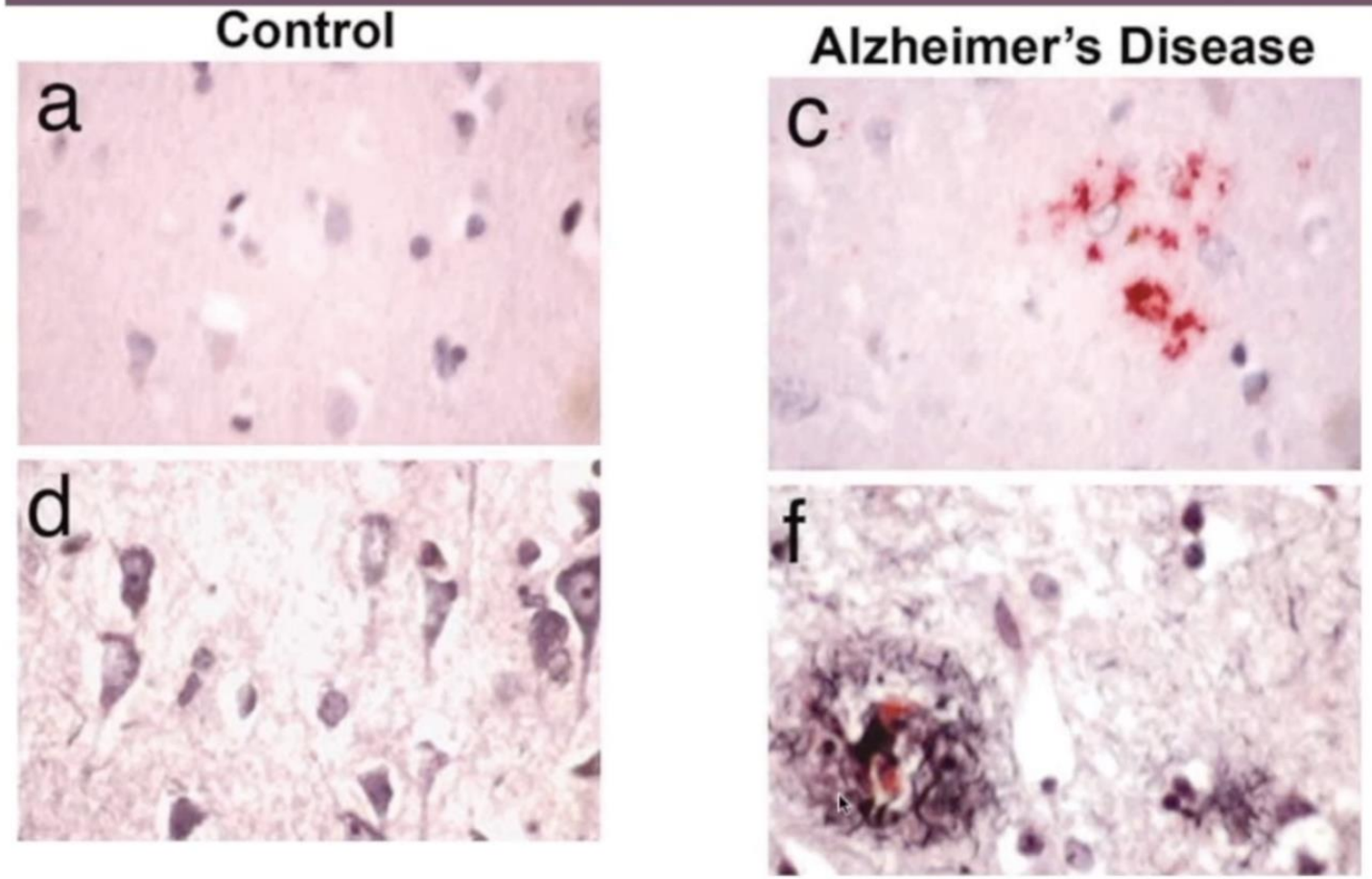
Look at the Whole Puzzle Not Just One Piece –

Other SNPs that significantly modulate risk for ApoE ε4 Individuals:

- Genes right next to Apo E4 can have additive effect
- Mitochondrial Pathways
- Inflammation Factors
- Cholinesterase Pathways



Butyrylcholinesterase (BCHE)



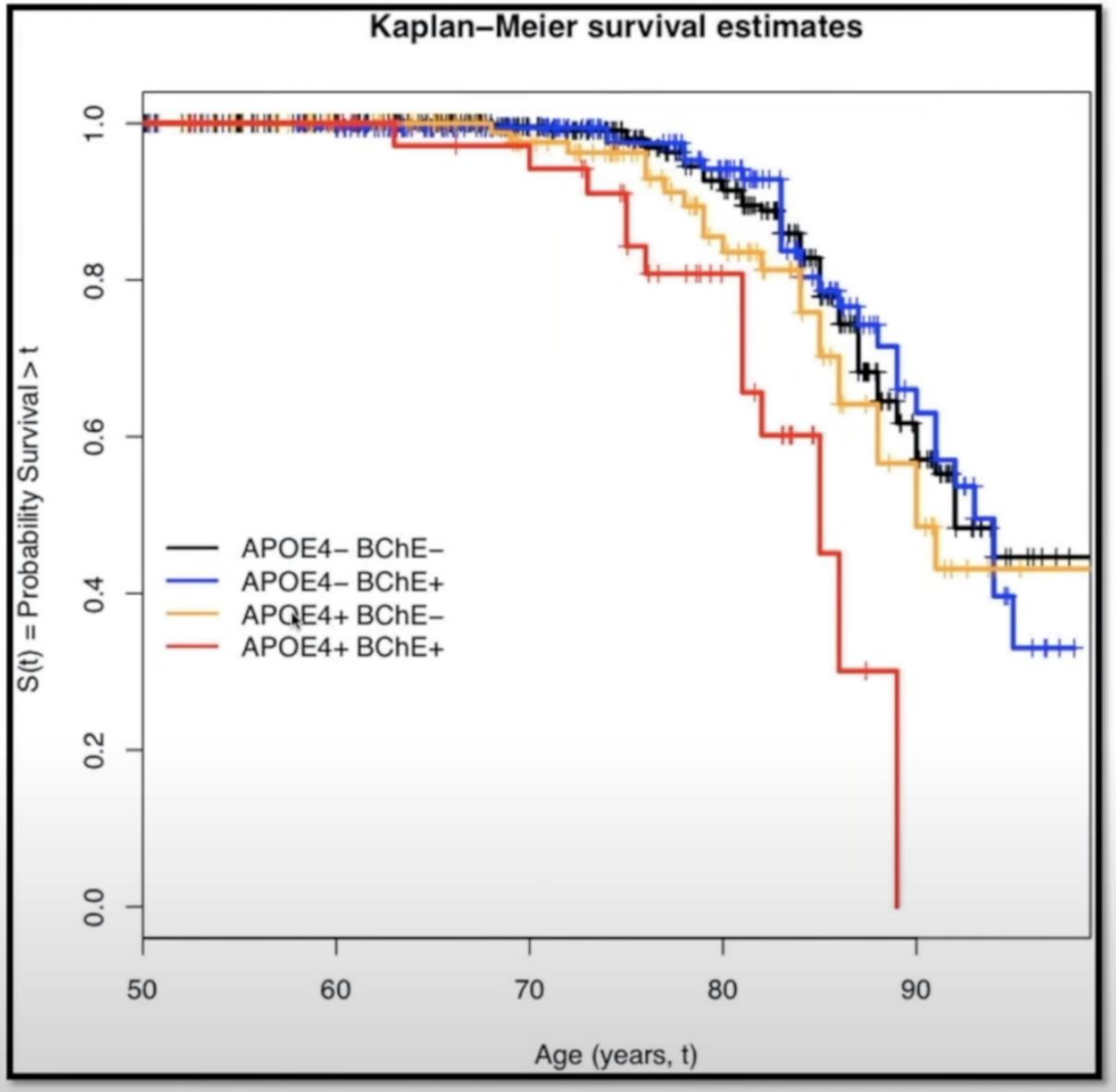
- BCHE normally helps to suppresses amyloid beta strands joining together to form the fiber like structures that gunk up the brain. People with the BCHE SNP are less effective at blocking the accumulation of those amyloid beta fibers or fibrils.

BChE- Good and Bad for Alzheimer Disease♦: The Butyrylcholinesterase Variant Confers Structurally Derived Risks for Alzheimer Pathology. *J Biol Chem*. 2009;284(25):e99926

Illustration from Rajendran et al. PNAS July 25, 2006 103 (30) 11172-11177

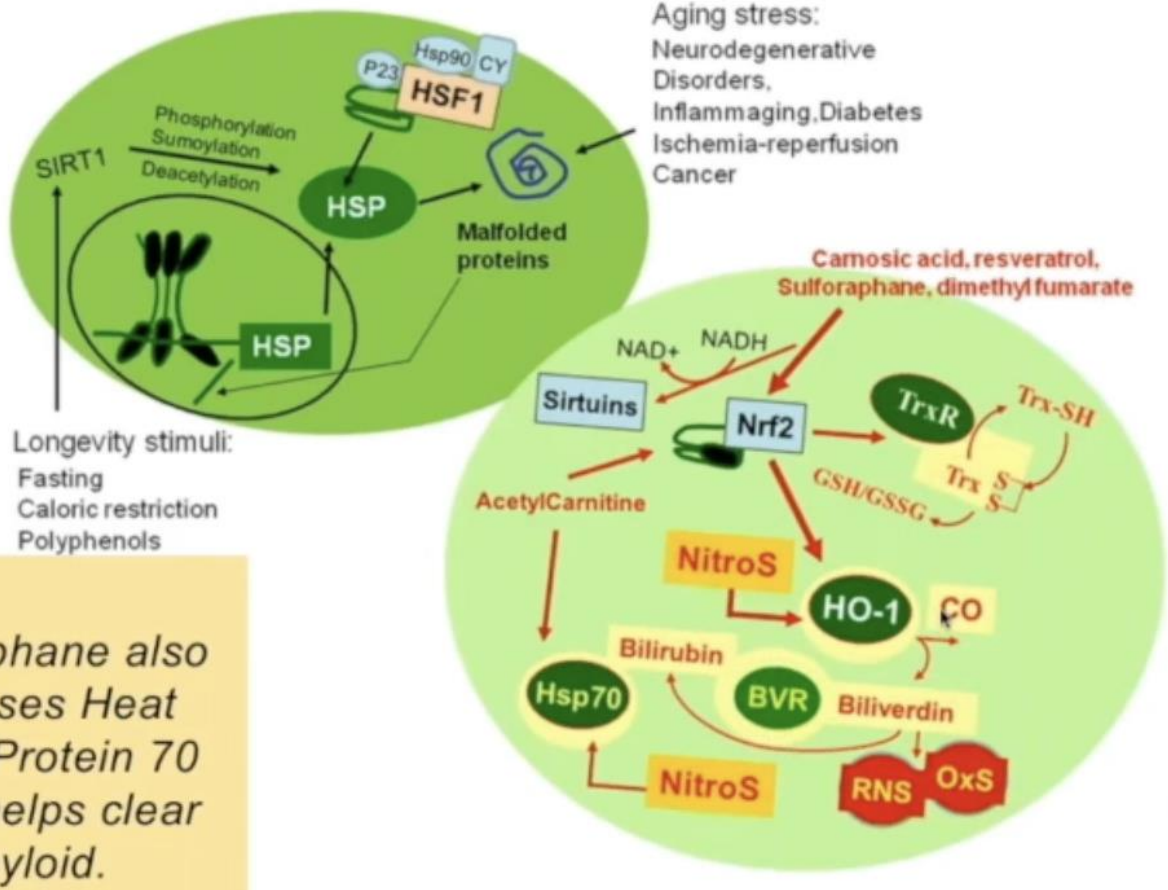
Presence of BCHE and ApoE Together **Doubled** Likelihood of Disease: 1.77 vs 3.36

2017 Baltimore Longitudinal Study Showed that LACK of BCHE cuts APOE4 RISK IN ½.



Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2017 13, P978-P979DOI: (10.1016/j.jalz.2017.06.1327)

Sulforaphane, Carnosic Acid and Resveratrol all Increase Nrf2 and decrease inflammation



Sulforaphane also increases Heat Shock Protein 70 which helps clear amyloid.

Above Image: Oxid Med Cell Longev. 2015;2015:781938. doi: 10.1155/2015/781938. Epub 2015 Jun 9

Datitilo S et al. Immunity & Ageing2015**12**:20 Heat Shock Proteins and hormesis in the diagnosis and treatment of neurodegenerative diseases.

TNF Alpha and ApoE4

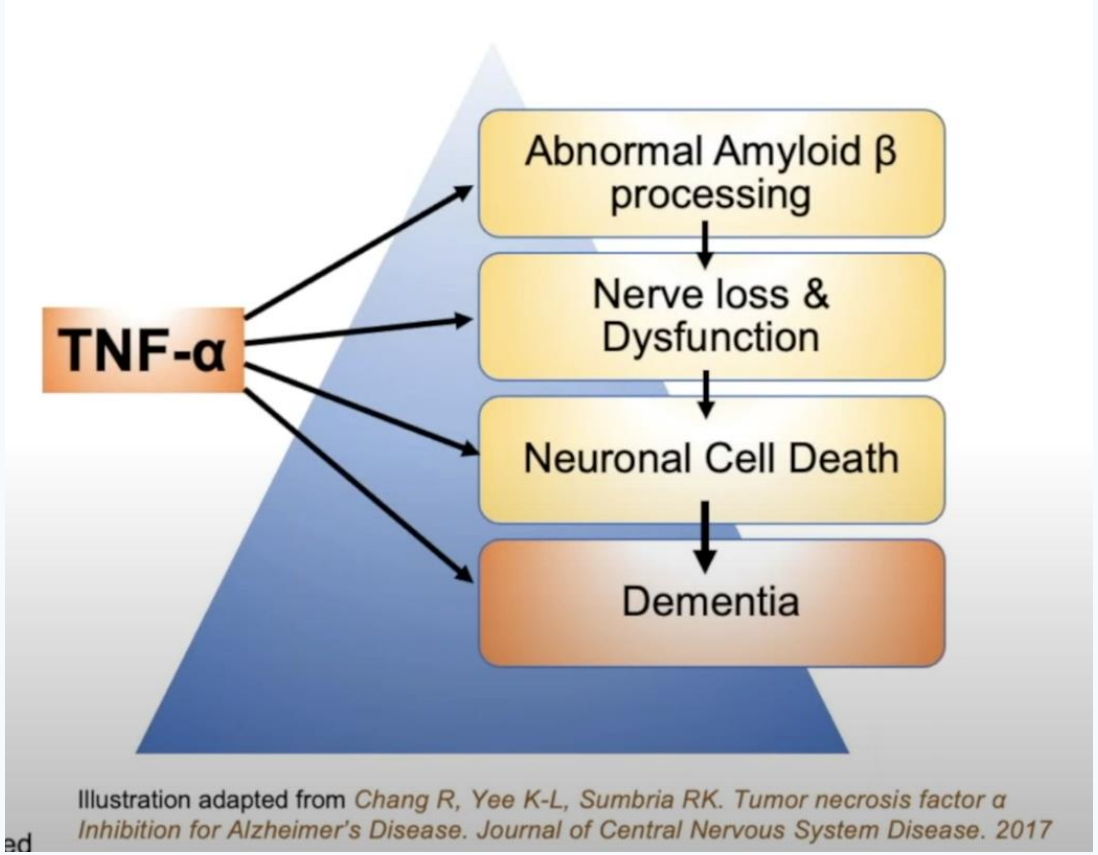


Illustration adapted from *Chang R, Yee K-L, Sumbria RK. Tumor necrosis factor α Inhibition for Alzheimer's Disease. Journal of Central Nervous System Disease. 2017*

- ApoE ε4 individuals already have high brain inflammation but when they have gene variants in this pathway it is exaggerated.
- TNF-α over activates the "garbage collector" (glial cells) in the brain and causes scarring and inflammation which leads to more cognitive decline
- There was even one study showing that this combination of ApoE ε4 variants and specific TNF-α variants can increase a person's risk of Alzheimer's disease over 6-fold.

Hericium erinaceus - Lion's Mane Mushroom Inhibits TNF-α and MORE

- Erinacine (lion's mane) reduced amyloid burden **38-40%.**
- Reduced size and number of plaques in animal models.
- Increased Insulin degrading enzyme **141.1-269%.**
- Other Erinacine induced nerve growth factors from **129-299%.**

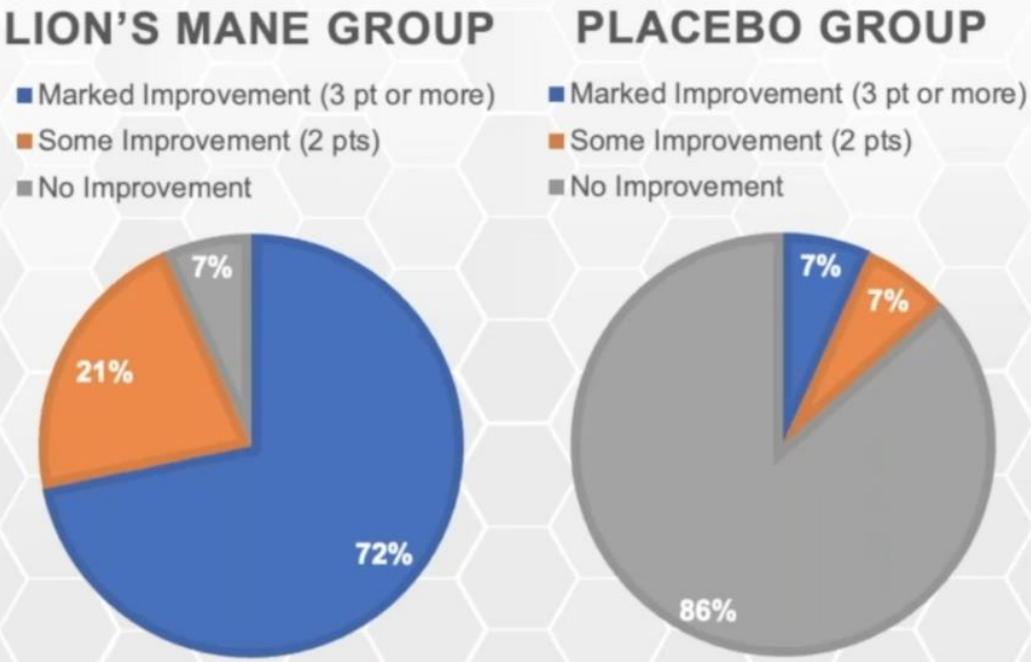
Lion's Mane Cognition Study

50-80 year old seniors with MCI

500 mg three times a day x 16 wk

- Increased scores on the cognitive function compared with the placebo group at by 8 weeks. Continued.
- Scores increased throughout study. 4 weeks after study ended, the scores again decreased significantly.

Increase in Dementia Scale In Lion's Mane Group



Mori K. et al: Phytother. Res. 23, 367–372 (2009)

ApoE ε4 is Found in Most Cases of Late Onset Alzheimer's

- Population attributable risk of Alzheimer's to the ApoC1- ApoE ε4 loci is about 70%
- **What about the other 30% of individuals with MCI and LOAD?**

Rachel is an ApoE 3/3 – So What is Going On?

Risk SNP	Gene	Risk Allele	Patient Allele	Variant (0, 1, 2)	Notes
rs42...	APOE	C	TT	0	**Apolipoprotein E (ε4).** Each C allele of this SNP correlates to having one APOE ε4 allele (Apo E4) [86]. • Apolipoprotein E supports both lipid transport and injury repair in the brain. Amyloid and lipid molecules attach to the APOE and are … [40]. • APOE ε4 also upregulates TNF-a and causes more inflammation [107] • APOE ε4 downregulates the production of the nerve growth factor BDNF which is important for forming new memory connections in the hippocampus [106]
rs16...	APOC1	I	DD	0	**Apolipoprotein C1**. This SNP is in the promoter region of APOC1 and is near the APOE gene. **NOTE: There has been no risk identified for individuals who carry this variant but DO NOT HAVE AN APOE ε4 variant [73].** • ApoC1 works in conjunction with APOE ε4 and is a significant contributing factor to whether or not an APOE ε4 individual is more prone to development of Alzheimer's [73].

So We Started Investigating...

- Cognition and Memory Pathway
- Leukoaraiosis and Hippocampal Atrophy Pathway
- Brain Ischemia Pathway
- Homocysteine and Methylation Pathway
- BDNF Pathway
- Heavy Metals & Detox Pathway
- Benzene, Pesticides and Other Toxins Pathway
- Estrogen Pathway
- Thyroid: Free T4 to Free T3 Conversion Pathway
- Copper and Zinc Pathway
- Choline Pathway
- Vitamin B12 Pathway

Rachel had 2 genes that increase risk: 2.5x Alzheimer's & 3.7x Vascular Dementia

APOE Independent Risk Factor:

- Address Methylation
- Address Inflammation

Gene	Risk Allele	Patient Allele	Variant (0, 1, 2)	Odds Ratio	Notes
MTHFR	A	AG	1	1.13	**Methylenetetrahydrofolate Reductase** • Enzyme involved in last step of the conversion of folic acid or dietary folate to methylfolate. Methylfolate is the fat-soluble form that crosses the blood brain barrier and is needed for the production of neurotransmitters. • **When combined with IL6 below has 2.5x OR** • IL6/MTHFR combination has also been associated with an increased risk of vascular dementia **(OR = 3.7).** • This SNP raises homocysteine levels by decreasing methylation of folic acid approximately 35% per copy.
IL6	C	CG	1	2.5	**Interleukin 6** • Pro-inflammatory cytokine.

MTHFR/IL6 is Major Vascular Dementia Risk

C677T Variant is in Riboflavin Binding Site

rs1801133	MTHFR C677T	A	AG	GA 44.8%	1	1.13 (1.13/1.18)	**Methylenetetrahydrofolate Reductase** (interpret in combination with IL6 below [41]) • Enzyme involved in last step of the conversion of folic acid or dietary folate to methylfolate [41]. • Methylfolate is the fat-soluble form of folic acid that crosses the blood brain barrier and is needed for making serotonin, norepinephrine, dopamine (all involved in depression) and acetylcholine (memory). • IL6/MTHFR combination (see bold below) has also been associated with an increased risk of vascular dementia (OR = 3.7) [41]. associated with elevated homocysteine and depression. Each copy of the minor allele corresponds to about 35% lower production of methylfolate [177]. • **OR = 2.5 is only applicable if an individual has 1 or 2 variants in this SNP and 1 or 2 variants in IL6 rs1800795 [41]. MTHFR rs1801133 | IL6 rs1800795 | Additive OR AA or AG | CC or CG | 2.50 ***Potential Interventions:*** *See homocysteine panel for full explanation. L-Methylfolate and address inflammation if IL6 SNP is present [130]. SNP shown to decrease MTHFR's affinity for riboflavin (its cofactor), so make sure gets adequate riboflavin [144].*

Interleukin 6

Interleukin 6 is an inflammatory cytokine involved in beta cell differentiation. Contributing factor to vascular dementia and many brain inflammatory states:

- Alzheimer's, Depression, Parkinson's & Multiple Sclerosis
- IL-6 contributes to the processing of Amyloid Precursor Protein and neurofibrillary tangle formation
- Higher IL-6 levels have been associated with cognitive decline

Many Studies on IL6 and Role in Alzheimer's and Vascular Dementia

There are dozens of studies that discuss IL6 and it's Role in Alzheimer's/Vascular Dementia

MTHFR (677 and 1298) and IL-6-174 G/C genes in pathogenesis of Alzheimer's and vascular dementia and their epistatic interaction

October 2011 · Neurobiology of aging 33(5):1003.e1-8

Genetic risk factors play an important role in the pathogenesis of Alzheimer disease (AD) and vascular dementia (VaD). In this case-control study, we examined C677T and A1298C (rs1801133 and rs1801131) polymorphism in the methylenetetrahydrofolate reductase (MTHFR) genes and their correlation with plasma levels of homocysteine (Hcy) in AD and VaD cases and evaluated the gene-gene interaction (epistasis) with IL-6-174 G/C (rs1800795). CC genotype was associated with elevated levels of plasma homocysteine (p = 0.004) as compared with genotype AA of rs1801131. In AD, we observed a significant (p = 0.04) association with C alleles of rs1801131. Regression analysis revealed that the presence of both rs1801133 T and rs1800795 C alleles increased the odds of developing AD by 2.5 and VaD by 3.7-fold. While rs1800795 (CC or GC) genotypes alone increased the odds of developing VaD by 2.2-fold, the presence

Biochemical blood markers support genomics: higher IL6 correlates with 1.81x cognitive decline

Neurology. 2014 Aug 5; 83(6): 486–493. PMCID: PMC4141998

doi: [10.1212/WNL.0000000000000665] PMID: 24991031

Interleukin-6 and C-reactive protein as predictors of cognitive decline in late midlife

Archana Singh-Manoux, PhD,[a] Aline Dugravot, MSc, Eric Brunner, PhD, Meena Kumari, PhD, Martin Shipley, MSc,

Results: In cross-sectional analysis, reasoning was 0.08 SD (95% confidence interval [CI] −0.14, −0.03) lower in participants with high compared to low IL-6. In longitudinal analysis, 10-year decline in reasoning was greater (*p*trend = 0.01) among participants with high IL-6 (−0.35; 95% CI −0.37, −0.33) than those with low IL-6 (−0.29; 95% CI −0.31, −0.27). In addition, participants with high IL-6 had 1.81 times greater

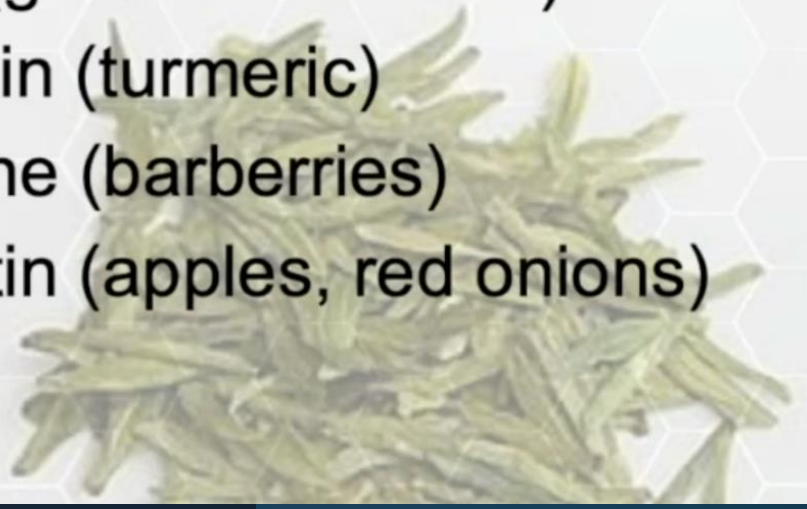
What can you do about MTHFR and IL6

MTHFR:

- Use a vitamin that contains L-methylfolate rather than plain folic acid
  - Dosing depends on if treating depression, cognition or just for prevention

IL-6 relates to brain inflammation. Lower with:

- Sulforaphane (broccoli sprouts)
- EGCG (green tea extract)
- Curcumin (turmeric)
- Berberine (barberries)
- Quercetin (apples, red onions)



Phytomedicine. 2021 Jul; 87: 153583.
Published online 2021 May 4. doi: 10.1016/j.phymed.2021.153583
PMCID: PMC8095027
PMID: 34033999

Sulforaphane inhibits the expression of interleukin-6 and interleukin-8 induced in bronchial epithelial IB3-1 cells by exposure to the SARS-CoV-2 Spike protein

Jessica Gasparello,[a] Elisabetta D'Aversa,[a] Chiara Pap
Alessia Finotti,[a,d,*] and Roberto Gambari[a,c,d,*]

Author information ▸ Article notes ▸ Copyright and Li

Cancer Prev Res (Phila). Author manuscript; available in PMC 2011 Apr 1.
Published in final edited form as:
Cancer Prev Res (Phila). 2010 Apr; 3(4): 484–494.
Published online 2010 Mar 16. doi: 10.1158/1940-6207.CAPR-09-0250
PMCID: PMC2853726
NIHMSID: NIHMS170519
PMID: 20233902

Sulforaphane Inhibits Constitutive and Interleukin 6 Induced Activation of Signal Transducer and Activator of Transcription 3 in Prostate Cancer Cells

Eun-Ryeong Hahm and Shivendra V. Singh

> Oxid Med Cell Longev. 2020 Sep 10:2020:4754195. doi: 10.1155/2020/4754195. eCollection 2020.

sclaimer

Sulforaphene Ameliorates Neuroinflammation and Hyperphosphorylated Tau Protein via Regulating the PI3K/Akt/GSK−3 β Pathway in Experimental Models of Alzheimer's Disease

Wen Yang [1], Yue Liu [2], Qing-Qing Xu [1], Yan-Fang Xian [1 3], Zhi-Xiu Lin [1 3 4]
Affiliations + expand

PMID: 32963694 PMCID: PMC7502131 DOI: 10.1155/2020/4754195
Free PMC article

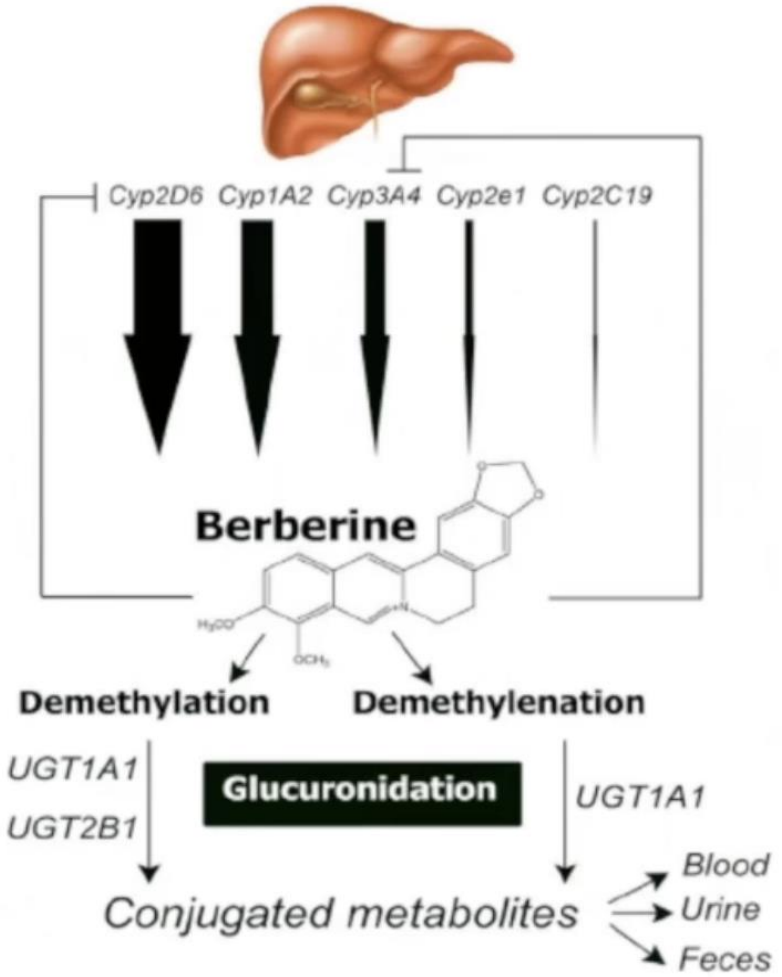
Berberine: Inhibits IL-6 mediated inflammation:

- Berberine: From Barberries
- Anti-inflammatory effects include - inhibiting IL-6 and TNF-α
- Helps protect against neuronal damage by decreasing Glia mediated inflammation
  - Decreases apoptosis & MMP-9
  - Decreases BBB permeability

HOWEVER, CAUTION AS CAN DECREASE CYP2D6, 2C9, and CYP3A4

CAUTION: Berberine and DRUG METABOLISM

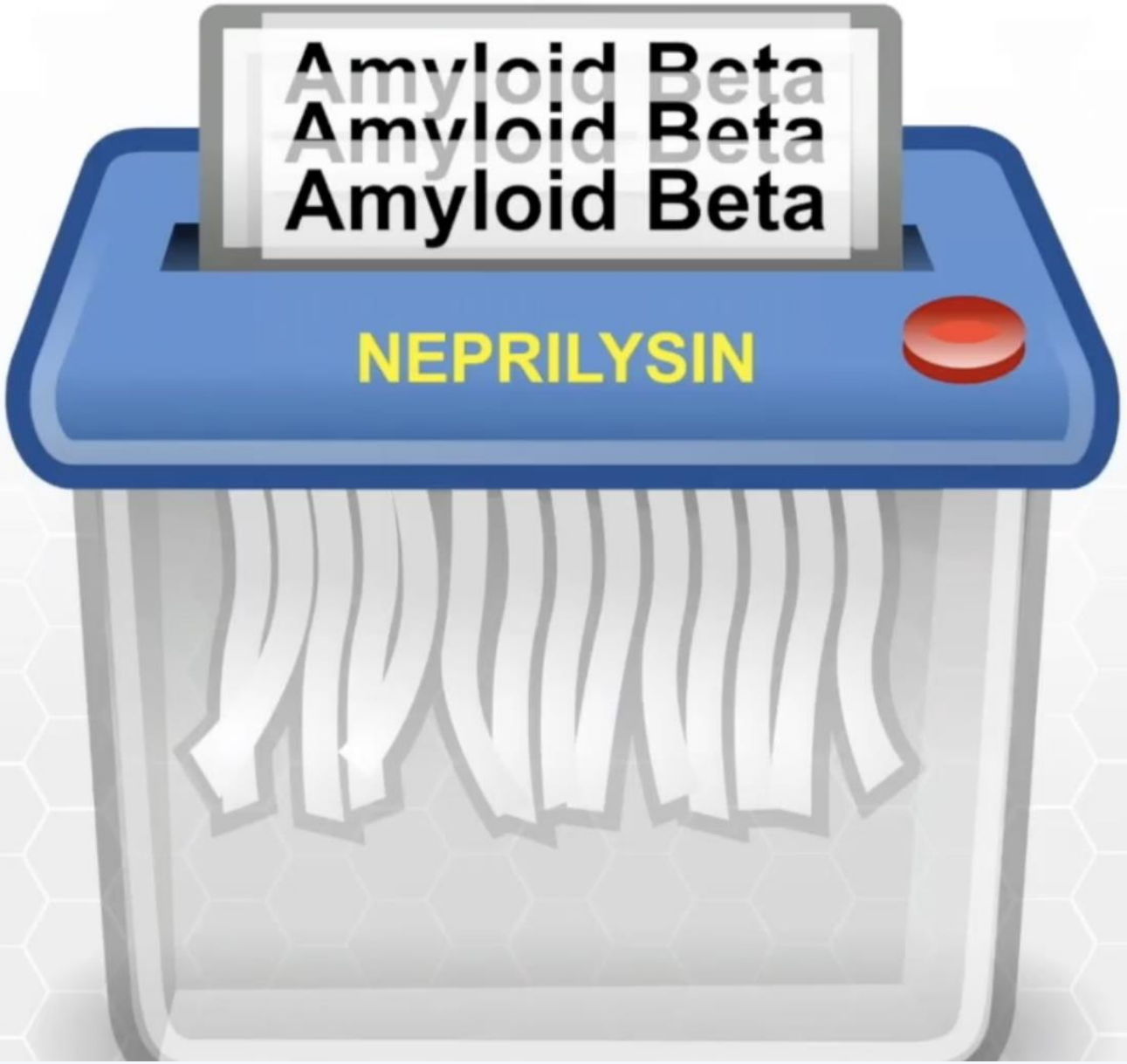
- **BERBERINE CAN DECREASE CYP2D6, 2C9, and CYP3A4 with typical dose of 1 gram a day**
  - Increased Dextromethorphan levels
  - Increased Losartan levels
  - Increased Midazolam levels



1) Eur J Clin Pharmacol. 2012 Feb;68(2):213-7. doi: 10.1007/s00228-011-1108-2. Epub 2011 Aug 26. Kaboli, P. Et al. June 2014

And Genetic Decreased Ability to Make Neprilysin

- Important Aβ degrading enzyme



Ashwagandha Increases Expression of Neprilysin

- Increases expression of the Aβ-degrading protease neprilysin (NEP) within 2 weeks
- Promotes neurite outgrowth in presence of Aβ-induced neurodegeneration
- Also promotes disassembly of toxic Aβ oligomers

ASHWAGANDHA AND MEMORY: HUMAN TRIALS

Improved cognitive and motor performance within 2 weeks

- Reaction times
- Choice discrimination (6%)
- Digit symbol substitution (7% improvement)
- Digit vigilance (3% improvement)
- Card sorting tests (6% improvement)

Population: Adult males on 500 mg twice a day

Promising studies for brain preservation and nerve regeneration in Alzheimer's animal models.

CAUTION: MILD BLOOD THINNER SO IF ON ANTICOAGULANTS MONITOR CAREFULLY OR DON'T USE OR LIMIT DOSE

Pharmacognosy Res. 2014 Jan;6(1):12-8. doi: 10.4103/0974-8490.122912. *Biol Pharm Bull.* 2014;37(6):892-7.

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ashwagandha and memory

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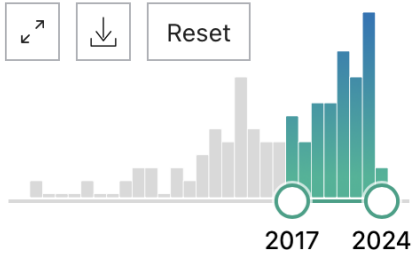

TEXT AVAILABILITY

51 results

Page 1 of 6

1

Cite

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Efficacy and Safety of **Ashwagandha** (**Withania** somnifera (L.) Dunal) Root Extract in Improving **Memory** and Cognitive Functions.

Choudhary D, Bhattacharyya S, Bose S.

J Diet Suppl. 2017 Nov 2;14(6):599-612. doi: 10.1080/19390211.2017.1284970. Epub 2017 Feb 21.

PMID: 28471731 Clinical Trial.

OBJECTIVES: Cognitive decline is often associated with the aging process. **Ashwagandha** (**Withania** somnifera (L.) Dunal) has long been used in the traditional Ayurvedic system of medicine to enhance **memory** and improve cognition. AIM: This pilot study was designe ...

“BDNF” a Brain Growth Factor- Like Fertilizer for the Brain – 4% of population

Rachel’s BDNF pathway:

	Risk or Benefit Allele	Prevalence	Variants	Notes
BDNF	T	4.13 %	2	**You have a genomic variant(s) in this "Brain-Derived Neurotrophic Factor" pathway.** • Variants are associated with lower BDNF levels and a higher risk of depression. • Consult with your clinician regarding possible 3 SNP combinatorial cognitive impairment risk.
BDNF	G	5.02 %	2	**You have a genomic variant(s) in this "Brain-Derived Neurotrophic Factor" pathway.** • Consult with your clinician regarding possible 3 SNP combinatorial cognitive impairment risk.
BDNF	C	3.99 %	2	**You have a genomic variant(s) in this "Brain-Derived Neurotrophic Factor" pathway.** • Consult with your clinician regarding possible 3 SNP combinatorial cognitive impairment risk.

Brain Derived Neurotropic Factor
BDNF = Like Fertilizer for the Brain, Helping it to Grow Well

About 4% of people have a BDNF combination that increases their risk of Alzheimer's 2.7-fold (almost the risk of the "APOE 4" Alzheimer's gene).

LOW BDNF associated with higher rates of Alzheimer's related depression.

Exercise Increases BDNF
Exercise Improves Cognition Outcomes

Int J Nurs Stud. 2018 Jan 4;79:155-164. doi: 10.1016/j.ijnurstu.2018.01.002. [Epub ahead of print]

The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis.

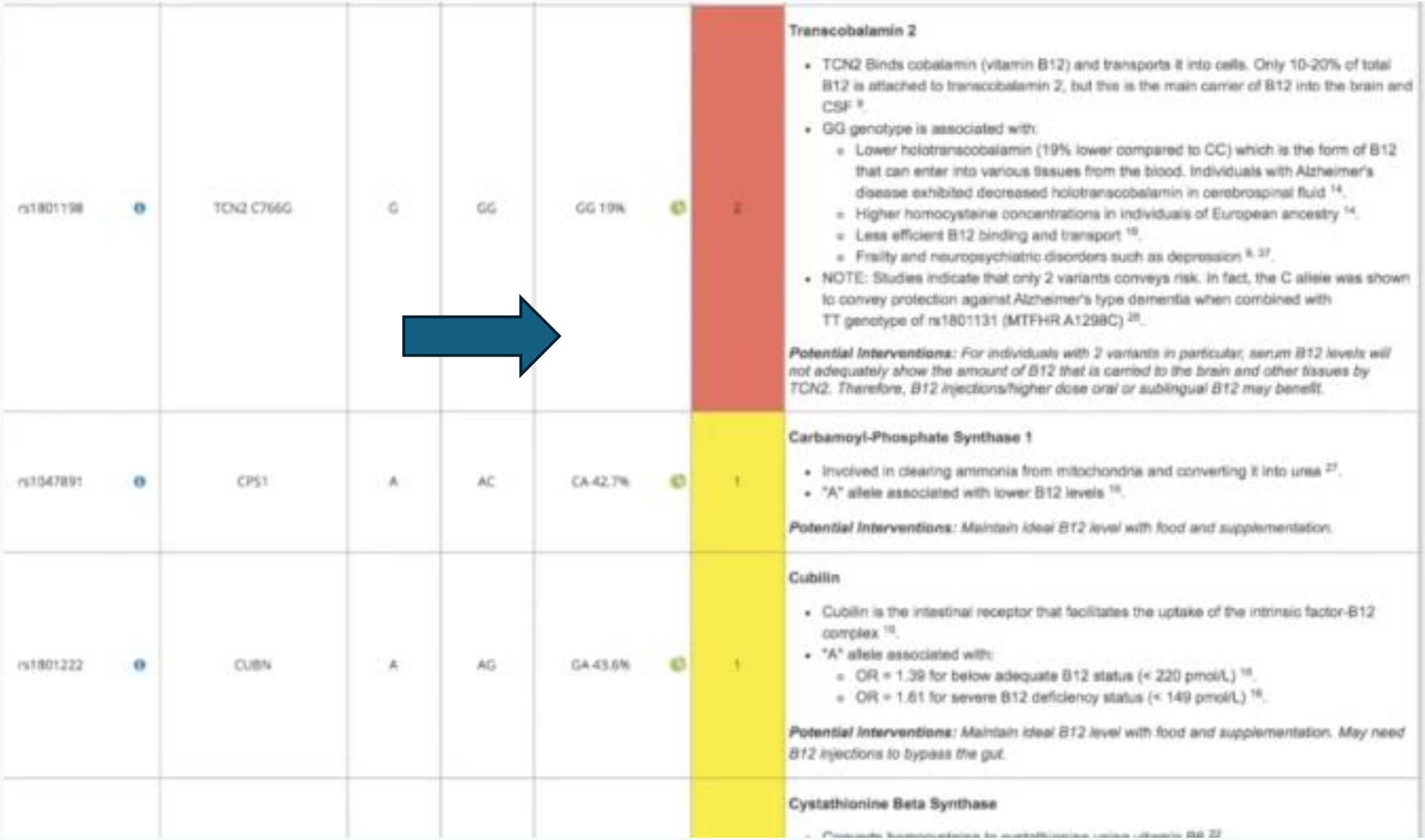
Front Neurosci. 2018 Feb 7;12:52. doi: 10.3389/fnins.2018.00052. eCollection 2018.

Exercise-Mediated Neurogenesis in the Hippocampus via BDNF.

Cell Tissue Res. 2018 Feb 15. doi: 10.1007/s00441-017-2782-x.

BDNF effects on dendritic spine morphology and hippocampal function.

TCN2: Binds B12 and carries into the cell



rs1801198	TCN2 C766G	G	GG	GG 19%	2	**Transcobalamin 2**
						• TCN2 Binds cobalamin (vitamin B12) and transports it into cells. Only 10-20% of total B12 is attached to transcobalamin 2, but this is the main carrier of B12 into the brain and CSF [9].
						• GG genotype is associated with:
						  ◦ Lower holotranscobalamin (19% lower compared to CC) which is the form of B12 that can enter into various tissues from the blood. Individuals with Alzheimer's disease exhibited decreased holotranscobalamin in cerebrospinal fluid [14].
						  ◦ Higher homocysteine concentrations in individuals of European ancestry [14].
						  ◦ Less efficient B12 binding and transport [15].
						  ◦ Frailty and neuropsychiatric disorders such as depression [9, 37].
						• NOTE: Studies indicate that only 2 variants conveys risk. In fact, the C allele was shown to convey protection against Alzheimer's type dementia when combined with TT genotype of rs1801131 (MTFHR A1298C) [28].
						Potential Interventions: *For individuals with 2 variants in particular, serum B12 levels will not adequately show the amount of B12 that is carried to the brain and other tissues by TCN2. Therefore, B12 injections/higher dose oral or sublingual B12 may benefit.*

rs1047891	CPS1	A	AC	CA 42.7%	1	**Carbamoyl-Phosphate Synthase 1** • Involved in clearing ammonia from mitochondria and converting it into urea [27]. • "A" allele associated with lower B12 levels [16]. ***Potential Interventions:*** *Maintain ideal B12 level with food and supplementation.*

rs1801222	CUBN	A	AG	GA 43.6%	1	**Cubilin**
						• Cubilin is the intestinal receptor that facilitates the uptake of the intrinsic factor-B12 complex [16].
						• "A" allele associated with:
						  ◦ OR = 1.39 for below adequate B12 status (< 220 pmol/L) [16].
						  ◦ OR = 1.61 for severe B12 deficiency status (< 149 pmol/L) [16].
						Potential Interventions: *Maintain ideal B12 level with food and supplementation. May need B12 injections to bypass the gut.*

						Cystathionine Beta Synthase

TCN2: Vitamin B12 carrier to Brain

Rachel had a significantly decreased ability to transport Vitamin B12 to his brain

- 20% of the body's B12 is carried by TCN2 (the rest is carried by TCN1).
- HOWEVER, TCN2 is the carrier for the brain so individuals with 2 variants can have normal blood B12 levels and low brain availability.
- HIGHER levels of B12 are needed to overcome.

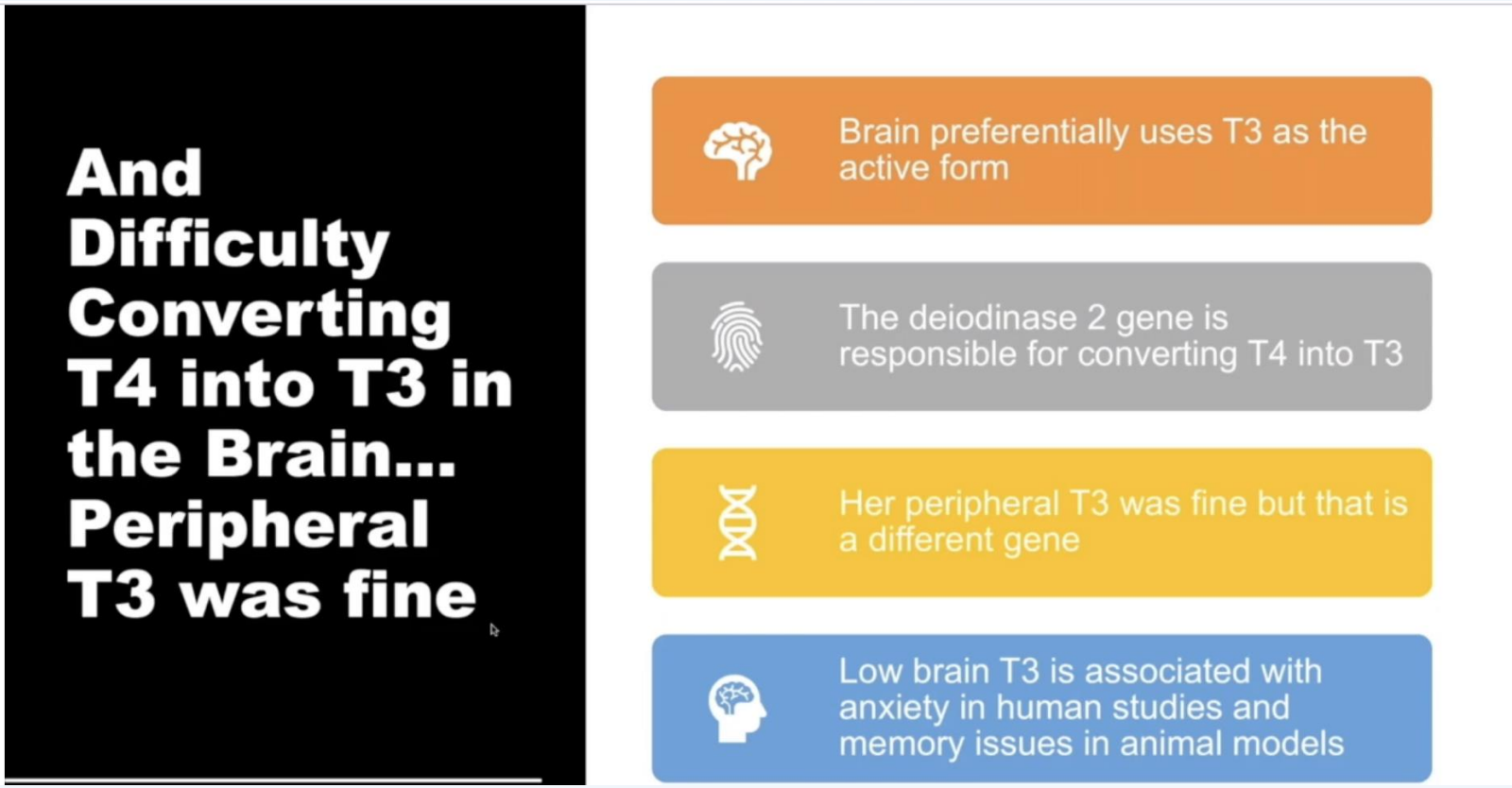
Rachel also had **DIO2 SNP:** Decreased ability to convert ft4 to ft3

Risk SNPs

Risk SNP	Gene	Risk Allele	Patient Allele	Prevalence	Variant (0,1,2)	Notes

rs225014	DIO2	C	CC	CC 14.1%	2	**Iodothyronine Deiodinase 2**
						• Decreases deiodination of free T4 (fT4) to free T3 (fT3) extracellularly and intracellularly [1, 3].
						• Additive effects with 2 variants.
						  ◦ Individuals had the greatest benefit in psychological well-being [3].
						  ◦ Post-thyroidectomy individuals had 58.3% reduction in fT3 and CT genotype had 36.5% reduction in fT3 [1].
						• Increased satisfaction seen with combo T3/T4 replacement [3].
						• Free T3 levels are affected, but not thyroid stimulating hormone (TSH) [1].
						• CC genotype has an OR 1.49 for depression and OR 1.56 for anxiety [3].
						• This SNP is associated with increased insulin resistance in T2DM [2].
						Potential Intervention: *Check free T3 in addition to TSH to evaluate this pathway. Liothyronine in addition to thyroxine or combination thyroxine/liothyronine replacement.*

What about thyroid?



JCI The Journal of Clinical Investigation

Type 2 deiodinase polymorphism causes ER stress and hypothyroidism in the brain

J Clin Invest. 2019;129(1):230-245. https://doi.org/10.1172/JCI123176.

Research Article | Endocrinology | Metabolism

Levothyroxine (LT4) is a form of thyroid hormone used to treat hypothyroidism. In the brain, T4 is converted to the active form T3 by type 2 deiodinase (D2). Thus, it is intriguing that carriers of the Thr92Ala polymorphism in the D2 gene (*DIO2*) exhibit clinical improvement when liothyronine (LT3) is added to LT4 therapy. Here, we report that D2 is a cargo protein in ER Golgi intermediary compartment (ERGIC) vesicles, recycling between ER and Golgi. The Thr92-to-Ala substitution (Ala92-D2) caused ER stress and activated the unfolded protein response (UPR). Ala92-D2 accumulated in the trans-Golgi and generated less T3, which was restored by eliminating ER stress with the chemical chaperone 4-phenyl butyric acid (4-PBA). An Ala92-Dio2 polymorphism–carrying mouse exhibited UPR and hypothyroidism in distinct brain areas. The mouse refrained from physical activity, slept more, and required additional time to memorize objects. Enhancing T3 signaling in the brain

Rachel was missing CLU SNP

Notes
Clusterin (Apolipoprotein J) • Clusterin affects brain inflammation, immune responses and amyloid clearance. It is a molecular chaperone that aids in protein folding. • Related to brain structure and function with C allele correlating to more rapid loss of tissue and quicker expansion of longitudinal ventricles. • *Combination effect significant for major alleles: Individuals who are not carriers of APOE ε4 allele and are CC (C= major allele) for rs11136000, and GG (G = major allele) for rs670139, odds ratio is 2.45 (i.e. zero variants for each SNP).* ***Potential Interventions:** If doesn't have CLU/MS4A4E protective variants - sulforaphane to increase heat shock protein 70.*
Membrane Spanning 4-Domains A4E • Exact function still being studied, but may affect amyloid fibril formation. • OR = 0.41 only applicable if TT for this SNP, TT for the CLU SNP, and also not a carrier of the APOE ε4 allele. • OR = 2.45 if GG for this SNP, CC for the CLU SNP, and also not a carrier of the APOE ε4 allele. ***Potential Interventions:** If doesn't have CLU/MS4A4E protective variants - sulforaphane to increase heat shock protein 70.*

CLU and MS4A4E

Don't forget to look for absence of benefits…important!

- Significantly increased risk (OR = 2.45) if homozygous major (i.e. no benefit alleles) for both SNPs, and **NOT** a carrier of APOE4.

CLU

- Promotes Amyloid-β efflux across the BBB
- Acts as a chaperone molecule (secreted by astrocytes in the brain) - binds soluble amyloid beta so can transport out of brain

Discoveries With A Genomic Clinical Decision Tool: Rachel

Word finding issues and family history of dementia

Gene variants discovered with one genomic swab:

MTHFR/IL6	MME	BDNF	**TCN2**	**DIO2**	**CLU absent**

Case of Rachel

- Curcumin, sulforaphane, drink green tea, higher omega 3 diet. L- methlyfolate (with riboflavin in B complex) (for MTHFR/IL6 combo, which triggers higher homocysteine, vascular inflammation)
- Ashwagandha bid – Amyloid, but also is COMT (MME - Low Neprilysn – Less Amyloid Processing down synaptogenic pathway)
- Vitamin B/Homocysteine; B complex (Neural B12 deficiency: Decreased ability to transport B12 to the brain)
- Increase Exercise, High Butyrate diet (Growth Factor Issues: Lower Mature BDNF)

How did Rachel Do?

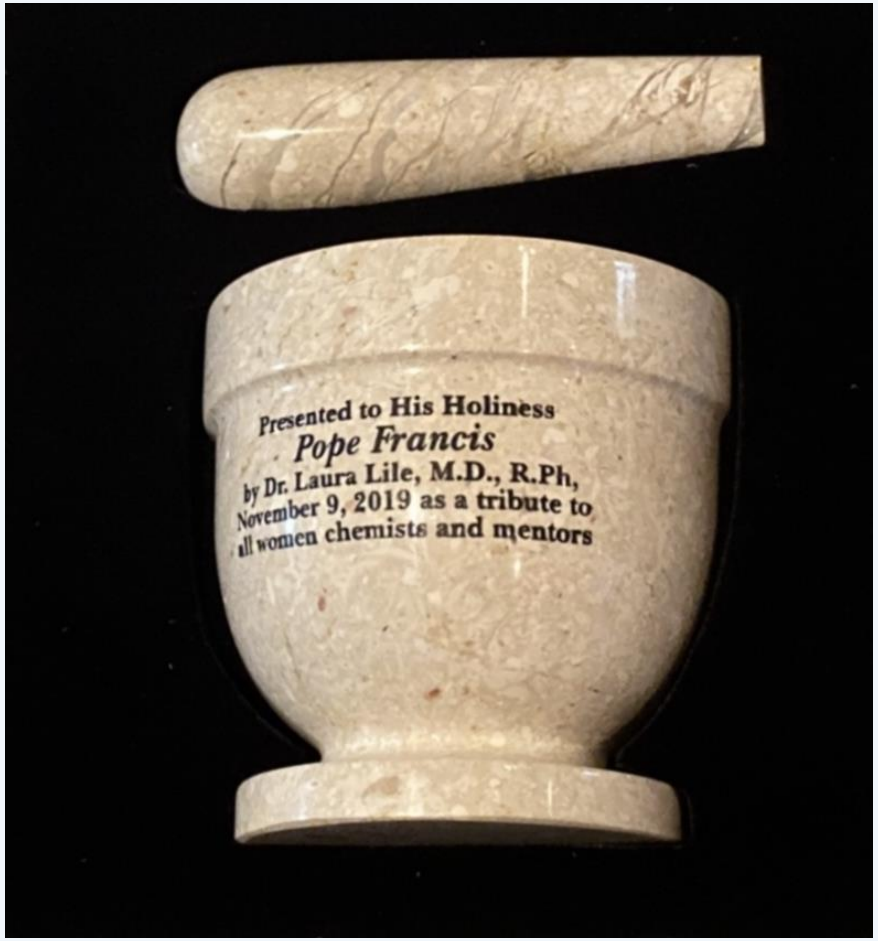
She did very well.

- Cognition back to baseline, able to teach graduate students, lecture and conduct her research without any problems.
- No need to substitute words.
- Anxiety and sleep improved as bonus.

Don’t be overwhelmed!

We never know what the future may hold.

Be the change and believe!



Thank you!

If you would like more information on genomic decision tools or have questions, please contact me at:

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