Intro to MTHFR

Folate Metabolism &
Its Far-Reaching Effects on Health

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"MTHF-er-*What?*"

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"I know, what *IS* MTHFR, anyway?"

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A vanity license plate maybe??

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- MTHFR is the enzyme that facilitates folate metabolism
- The MTHFR enzyme can be negatively affected by common defects in the gene that produces it
- The percentage of our population estimated to have one or more MTHFR defects is between 40-60%

MTHFR stands for "methylenetetrahydrofolate reductase"

- Vitamin B9
- Most plentifully found in raw leafy greens – cooking rapidly destroys folate
- Over 150 forms of folate – in medicine we use three terms:
  - Folic acid
  - Folinic acid
  - Methylfolate

Folate – Latin"folium" - LEAF

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"The functions of folate in human physiology are relatively simple, but the implications of their activity (and dysfunction) can be profound and far-reaching."

The Surprising Significance of Folate

From *Herb, Nutrient and Drug Interactions* by Stargrove et al

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- Synthesis of nucleic acids (for DNA production and repair and tRNA)
- Single carbon metabolism (methylation)
- Interconversion of amino acids (for neurotransmitter production and detoxification)
- Formation and maturation of RBC, WBC, and platelet production

Functions of Folate

From *Herb, Nutrient and Drug Interactions* by Stargrove et al

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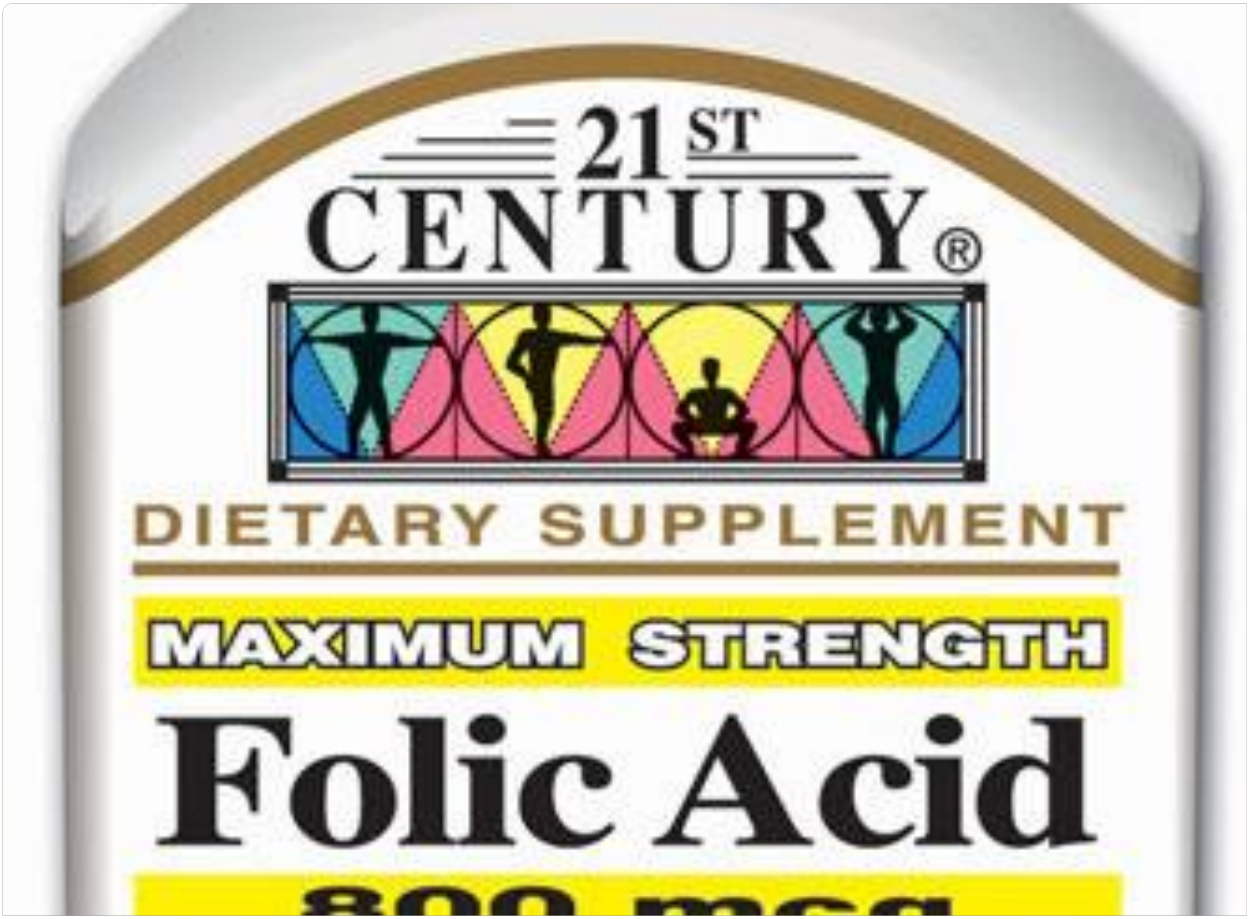

No – folic acid is synthetic. It is used in fortified foods because it is stable and has a long shelf-life. It is also the form most commonly used in nutritional supplements.

Folic acid is completely worthless until it is broken down into L-methyltetrahydrofolate (L-MTHF or 5-MTHF), the form the body can use.

The rate-limiting step in this conversion is the MTHFR enzyme

Is "folic acid" the same as – or at least equal to - natural folate?

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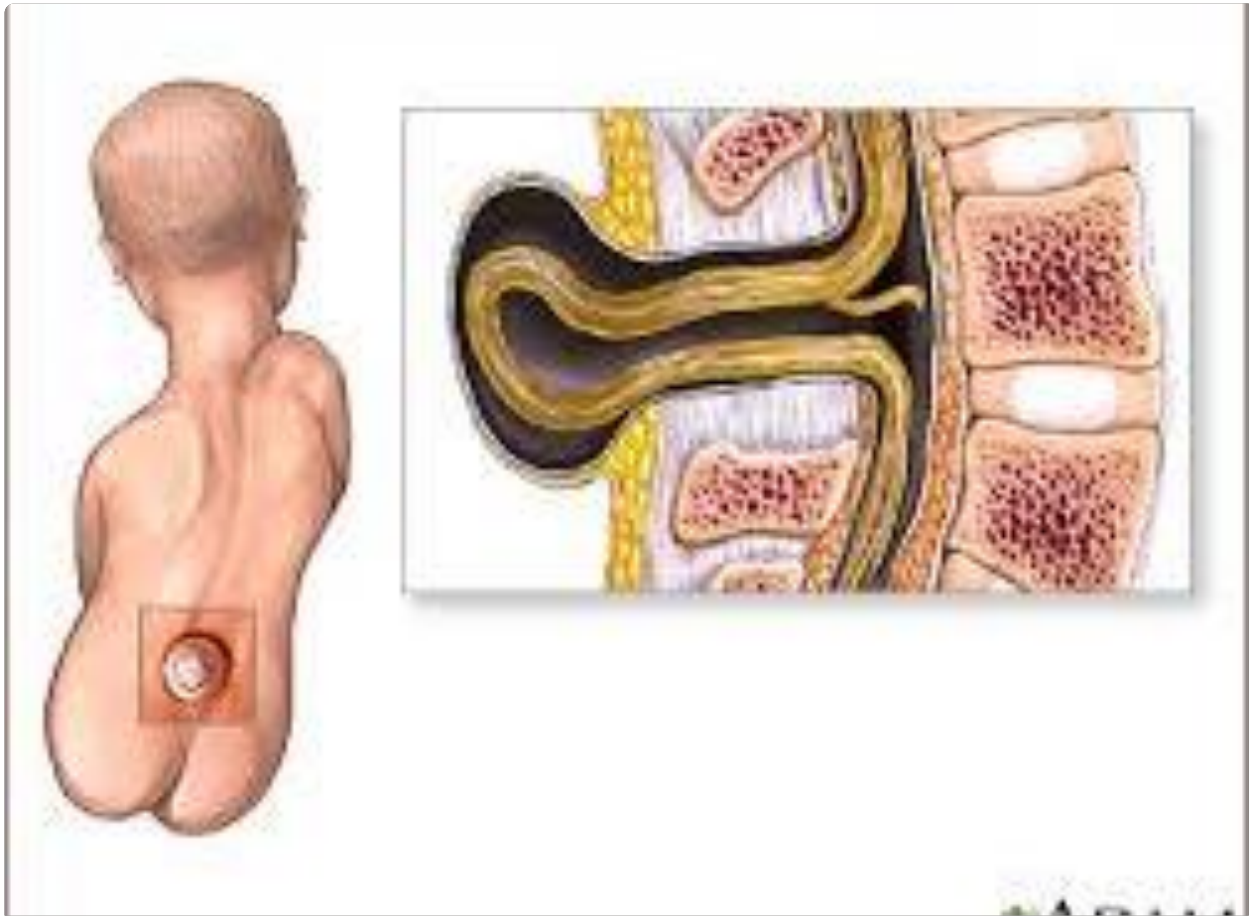

In **January 1998**, the FDA added a requirement that folic acid be added to breads, cereals, and other products that use enriched flour. These fortified foods include most enriched breads, flours, corn meals, rice, noodles, macaroni, and other grain products.

In the United States we can't get away from folic acid in the conventional diet

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Bread Label Nelson, BC

Nutrition Facts
Valeur nutritive

Per 1 slice (28 g)
pour 1 slice (28 g)

Calories 90

* DV = Daily Value
VQ = valeur quotidienne

Amount / Teneur	% DV / % VQ *	Amount / Teneur	% DV / % VQ *
Fat / Lipides 1.5 g	**3 %**	**Carbohydrate / Glucides** 15 g	**5 %**
Saturated / saturés 0.5 g + Trans / trans 0 g	**2 %**	Fibre / Fibres 1 g	6 %
		Sugars / Sucres 1 g	
Cholesterol / Cholestérol 0 mg		**Protein / Protéines** 3 g	
Sodium / Sodium 110 mg	**5 %**		
Vitamin A / Vitamine A	0 %	Vitamin C / Vitamine C	4 %
Calcium / Calcium	0 %	Iron / Fer	6 %

INGREDIENTS: * whole spelt flour/*farine d'epeautre entier, water/eau, *spelt flour/*farine d'epeautre, *palm fruit oil/*huile de palme fruit, *flax seed/*graine de lin, *cane sugar/*canne a' sucre, Leavening Agents, Yeast, Baker's, Compressed, sea salt / sel de mer, *apple cider vinegar/*vinaigre de cidre de pomme, * certified organic / * certifie' de culture biologique
INGRÉDIENTS: Leavening Agents, Yeast, Baker's, Compressed

Bread Label USA

Nutrition Facts
Serving Size 1 slice (55g)
Servings Per Container About 9

Amount Per Serving

Calories 200	Calories from Fat 90
	% Daily Value*
Total Fat 10g	**15%**
Saturated Fat 4g	**20%**
Trans Fat 0g	
Cholesterol 40mg	**13%**
Sodium 170mg	**7%**
Total Carbohydrate 24g	**8%**
Dietary Fiber 1g	**4%**
Sugars 13g	
Protein 3g	

Vitamin A 6%	•	Vitamin C 20%
Calcium 2%	•	Iron 6%
Thiamin 10%	•	Riboflavin 6%
Niacin 6%	•	Folate 6%

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Saturated Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

In the US we can only avoid ingestion of folic acid from our diet by avoiding all commercial breads, cereals, etc.

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“So…what’s the big deal?”

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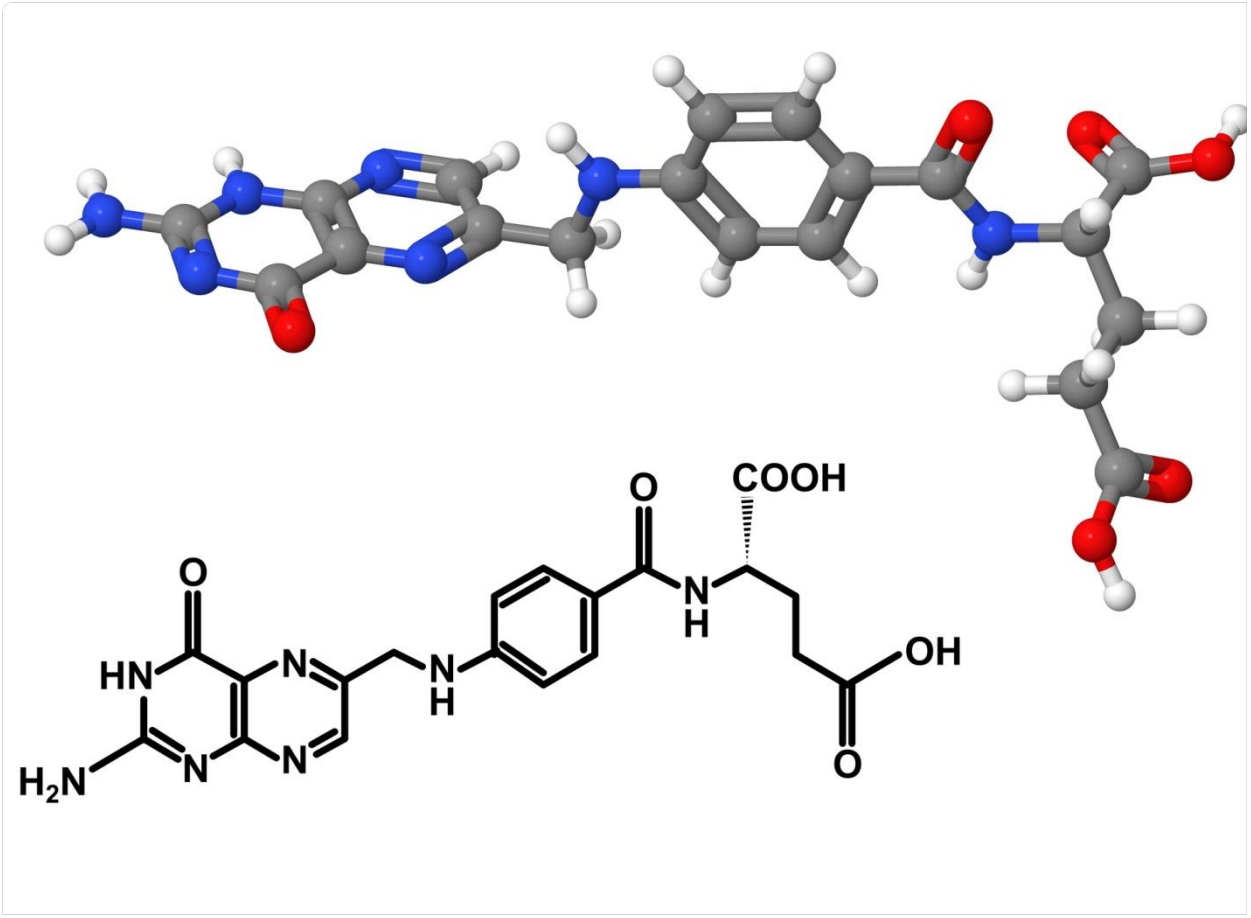

This means that if you have impaired folate metabolism and try to overcome it simply by increasing folate –containing foods and/or supplementing with L-MTHF, the L-MTHF will be upstaged by folic acid and continue to impair the process.

Folic acid competes with natural folate in the methylation pathway and wins…

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My Dad… always ahead of his time!

My late father, compounding pharmacist and clinician E. George Roentsch, was always several steps ahead of the rest of us. Here he is in 2005 at a New Year's Eve party. C'mon, isn't that what we all do at New Year's Eve parties???

If you could see the page better you would see that he is looking at a molecular diagram, and the title of the article is:

5-Methyltetrahydrofolate

Go Dad! "You might have spoken up, you know?!"

In recent years folic acid has been linked to increased cancer risk. Serum folic acid is often found to be high in people with methylation impairment, a problem that results from – but is not limited to – MTHFR defects.

Folic acid has been shown to reduce natural killer cell activity.

By the way…

J Nutr. 2006 Jan;136(1):189-94.

Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women.

Troen AM[1], Mitchell B, Sorensen B, Wener MH, Johnston A, Wood B, Selhub J, McTiernan A, Yasui Y, Oral E, Potter JD, Ulrich CM.

Author information

Abstract

Folic acid (FA) supplements and food fortification are used to prevent neural tube defects and to lower plasma homocysteine. Through exposure to food fortification and vitamin supplement use, large populations in the United States and elsewhere have an unprecedented high FA intake. We evaluated dietary and supplemental intakes of folate and FA in relation to an index of immune function, natural killer cell (NK) cytotoxicity, among 105 healthy, postmenopausal women. Among women with a diet low in folate (<233 microg/d), those who used FA-containing supplements had significantly greater NK cytotoxicity (P = 0.01). However, those who consumed a folate-rich diet and in addition used FA supplements > 400 microg/d had reduced NK cytotoxicity compared with those consuming a low-folate diet and no supplements (P = 0.02). Prompted by this observation, we assessed the presence of unmetabolized FA in plasma as a biochemical marker of excess FA. Unmetabolized folic acid was detected in 78% of plasma samples from fasting participants. We found an inverse relation between the presence of unmetabolized FA in plasma and NK cytotoxicity. NK cytotoxicity was approximately 23% lower among women with detectable folic acid (P = 0.04). This inverse relation was stronger among women >or= 60 y old and more pronounced with increasing unmetabolized FA concentrations (P-trend = 0.002). Because of the increased intake of FA in many countries, our findings highlight the need for further studies on the effect of long-term high FA intake on immune function and health.

PMID: 16365081 [PubMed - indexed for MEDLINE] Free full text

Converting folic acid to 5-MTHF, the methylated form, requires the work of:

- Two functioning enzymes
  - MTHFR
  - MTHFD1
- Vitamins, Minerals, and pH
  - B2
  - B3
  - B6
  - B12
  - Vitamin C
  - Zinc (for absorption)
  - Acidic environment – hydrochloric acid (for absorption)

Converting folic acid to 5-MTHF

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"What *IS* methylation, anyway??"

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*"Methylation is the act of taking a single carbon and three hydrogens, namely a **methyl group**, and having it attach itself to an enzyme in your body. When this methyl group attaches to an enzyme, the enzyme performs an action. A common action performed by methylation that you appreciate daily is the **breakdown of histamine**. A methyl group is made by the methylation pathway and it floats around until it finds a specific enzyme to bind to. In this case, the methyl group binds to histamine. When a methyl group binds to histamine, histamine breaks apart and goes away."* - Ben Lynch, ND

METHYLATION

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"You can now figure out what happens if your methylation pathway is not producing enough methyl groups in this case. Your histamine does not break apart and, thus, your histamine levels increase, causing your nose to run and eyes to itch."

Ben Lynch, ND

"UNDER-METHYLATION MISERY"

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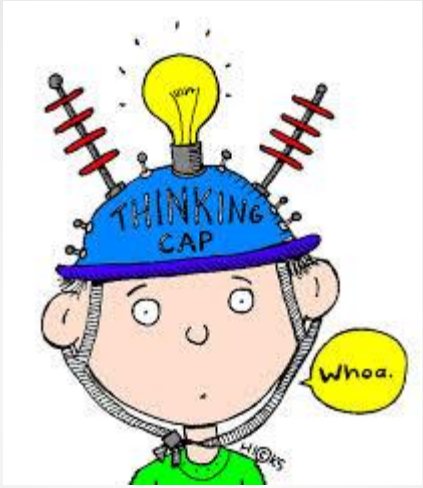

"Hmm…Let me wrap my head around this…"

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Picture methylation as a computer program continuously scanning your computer's hard drive, detecting errors and fragments, fixing, cleaning, and keeping your computer running like a well-oiled machine.

THAT'S WHAT METHYLATION DOES FOR OUR DNA

Think of methylation like this…

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“PCMatic.com!”

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- The Role of DNA Methylation in Cancer
- Ranjani Lakshminarasimhan and Gangning Liang
- Author information Copyright and License information PMC Disclaimer
- Abstract
- The malignant transformation of normal cells is driven by both genetic and epigenetic changes. With the advent of next-generation sequencing and large-scale multinational consortium studies, it has become possible to profile the genomes and epigenomes of thousands of primary tumors from nearly every cancer type. From these genome-wide studies, it became clear that the dynamic regulation of DNA methylation is a critical epigenetic mechanism of cancer initiation, maintenance, and progression. Proper control of DNA methylation is not only crucial for regulating gene transcription, but its broader consequences include maintaining the integrity of the genome and modulating immune response. Here, we describe the aberrant DNA methylation changes that take place in cancer and how they contribute to the disease phenotype. Further, we highlight potential clinical implications of these changes in the context of prognostic and diagnostic biomarkers, as well as therapeutic targets.

The role of DNA methylation in cancer

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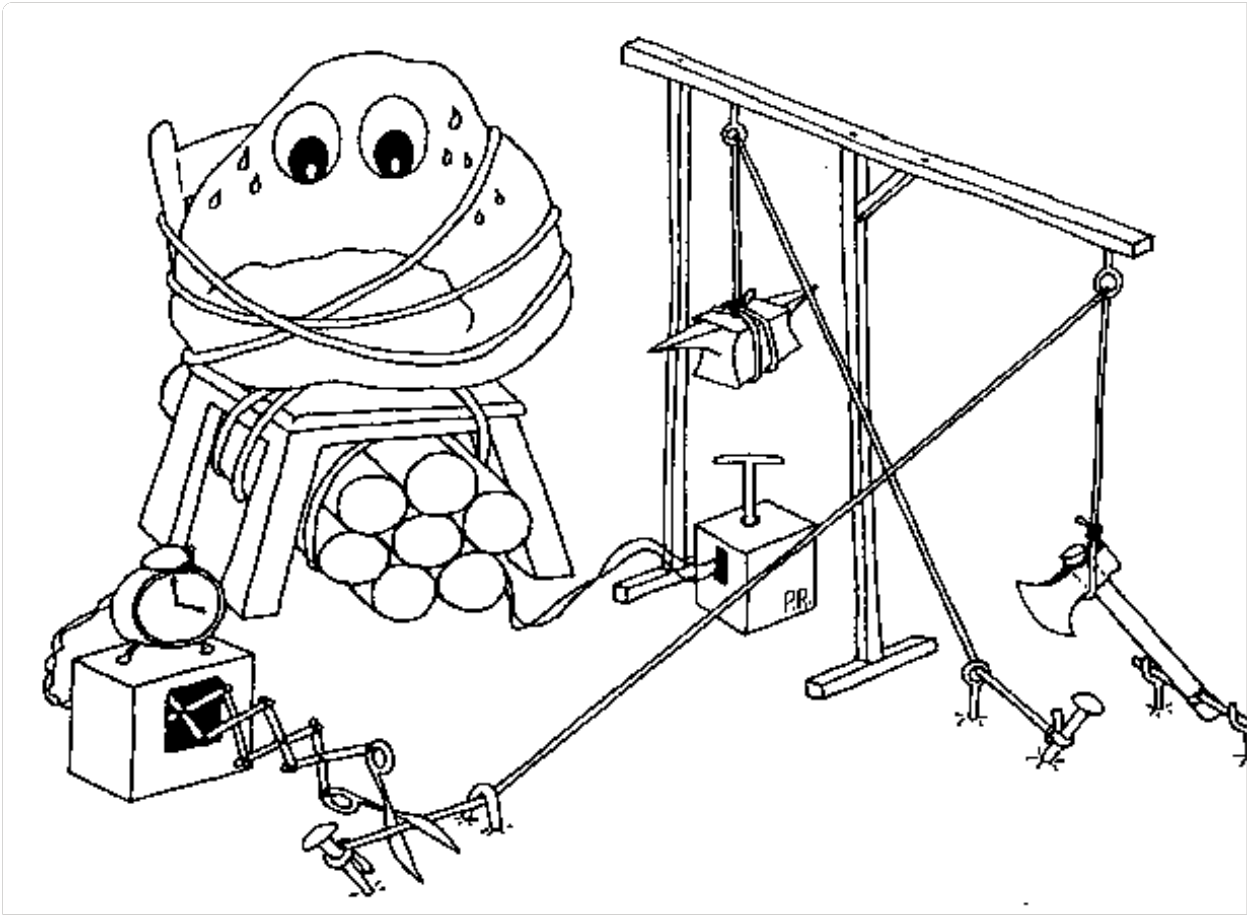

One of the very important results of successful methylation is the raising of glutathione levels. The tripeptide glutathione is the most potent catalyst of programmed death to mutant cells, commanding them to die before they can create more like their ***slimy, nasty selves***.

One of the important benefits of methylation is induction of APOPTOSIS

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…Think of methylation as fairies with "wondrous" wands that create "things" like neuro-transmitters and then go about zapping them to life!

And think of methylation THIS way…

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- Turn on and off genes (gene regulation)
- Process chemicals and toxins (biotransformation)
- Build neurotransmitters (dopamine, serotonin, norepinephrine)
- Process hormones (estrogen)
- Build immune cells (T-cells, NK-cells)
- DNA and RNA synthesis (thymine aka 5-methyluracil)
- Produce energy (CoQ10, carnitine, ATP)
- Produce protective coating on nerves (myelination)

Functions of Methylation

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MTHFR, Methylation, and Health

Many conditions of health and ill health can be traced back to here…

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Diabetes – Cancer – Pulmonary Embolism – Cleft Palate – Autism – Parkinson's – Neural Tube Defects – Atherosclerosis – Immune Deficiency – ADD/ADHD – Multiple Sclerosis – Alzheimer's – Dementia – Chemical Sensitivity – Congenital Heart Defects – Fibromyalgia – Depression – Alcoholism – Addictive Behaviors – Insomnia – Down Syndrome – Chronic Viral Infection – Thyroid Dysfunction – Neuropathy – Migraine - Recurrent Miscarriages – Infertility – Anxiety – Schizophrenia – Bipolar Depression – Eating Disorders – OCD - Allergies – Asthma - Psoriasis – Crohn's Disease - IBD – Celiac Disease – Gluten Intolerance & Other Food Intolerance

SOME **of the conditions that can be related to under-methylation and MTHFR defects**

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MTHFR Defects

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- Most Common
  - **C677T – identified in 1995**
  - **A1298C – identified in 2001**
- There are 7 other common defects
- 34 rare defects recognized as of 2003
- Other defects in the methylation pathway have been identified

677 & 1298 indicate their positions along the gene strand

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- Associated with elevated homocysteine
- Increase in heart disease
- Increased stroke
- Increased DVT
- Peripheral neuropathy
- Placental vascular problems (stillbirth)
- Preeclampsia, neural tube defects, cleft palette

C677T Defect
Some Prominent Features

But also found in some cases to strongly correlate with the C677T defect are psychiatric conditions such as:

- Schizophrenia
- Depression
- Bipolar disorder

"This meta-analysis demonstrates an association between the *MTHFR* C677T variant and depression, schizophrenia, and bipolar disorder, raising the possibility of the use of folate in treatment and prevention."

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- Depression, anxiety, IBS
- Fibromyalgia
- Chronic fatigue
- Migraine
- Dementia
- Nerve pain
- Schizophrenia
- Parkinson's
- Tetrahydrobiopterin (BH4) problems

A1298C Defect
Some Prominent Features

- Don’t clear heavy metals well
- Symptoms tend to worsen over time
- Cancer risk increased
- Renal failure
- Addiction potential
  - Drugs/Alcohol
  - Videogames
  - Pornography

Symptoms Related to Both C677T & A1298C

Heterozygous Defect

- One of the gene pair affected
- Methylation drops to 55-70% of normal

Homozygous Defect

- Both genes affected
- Methylation drops down to 7-10% of normal

Heterozygous vs. Homozygous

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Inheriting one defective gene in both the C677T and A1298C polymorphisms, resulting in:

- Symptoms of both defects
- Symptoms more severe
- Blood clots prevalent
- 98% of autistic persons tested are positive for this MTHFR anomaly

The Worst Combination "Compound Heterozygous"

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March 31, *2008*

"Julie Gerberding Admits on CNN that Vaccines can Trigger Autism"

*"This weekend Julie Gerberding, the head of the CDC, appeared on Dr. Sanjay Gupta's show, House Call, and explained that vaccines can trigger autism in **a vulnerable subset** of children."*

Autism-Vaccination Association MTHFR?

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So if we know it's broken, how do we fix it?

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A very good question, but, alas, one size does not fit all! However…

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- Clean up the diet and environment to reduce demand for methyl groups
- Improve bowel performance before beginning detox
- Address any presence of yeast overgrowth
- Eliminate or at least reduce ingestion of folic acid in food
- Use nutrients to assist in achieving successful methylation
  - Active form of folate (methyl or other if seems a better fit but no folic acid)
  - Active form of B12 (methylcobalamin, adenosylcobalamin, or hydroxocobalamin – depending on the person – no cyanocobalamin)
  - Possibly methyl donors such as TMG or SAM-e
  - S-acetyl-l-glutathione
  - Trace mineral support
  - Vitamins B2, B6
  - If high histamine is a problem a low-histamine diet and nutrients that help break down histamine

The "Big Picture" Basics

How Can I Use this Information Right Now to Improve Outcome for My Patients?

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TEST!

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Why is it so important to know my Patients' MTHFR status?

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- Antacids (deplete B12)
- • Cholestyramine (deplete cobalamin and folate absorption) – common in gallbladder issues during pregnancy
- • Colestipol (decrease cobalamin and folate absorption)
- • Methotrexate (inhibits DHFR – dihydrofolate reductase – converts dihydrofolate to tetrahydrofolate)
- • Nitrous Oxide (inactivates MS)
- • Niacin (depletes SAMe and limits pyridoxal kinase = active B6) useful during times of over-methylation
- • Theophylline (limits pyridoxal kinase = active B6)
- • Cyclosporin A (decreases renal function and increases Hcy)
- • Metformin (decreases cobalamin absorption)
- • Phenytoin (folate antagonist)
- • Carbamazepine (folate antagonist)
- • Oral Contraceptives (deplete folate)
- • Antimalarials JPC-2056, Pyrimethamine, Proguanil (inhibits DHFR)
- • Antibiotic Trimethoprim (inhibits DHFR)
- • Ethanol
- • Bactrim (inhibits DHFR)
- • Sulfasalazine (inhibits DHFR)
- • Triamterene (inhibits DHFR)

Common Drugs to Avoid

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Maybe a Great Place to Start?

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Right along with PKU

Know immediately if this new life has impaired ability to handle medical interventions such as vaccination and nitrous oxide anesthesia, dietary concerns such as fortified cereals, and more.

Make this a part of his or her medical chart for life!

Why not add the MTHFR test to Every Newborn's First Blood Draw?

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- Petition FDA to remove the requirement to fortify foods with folic acid
- Educate healthcare practitioners regarding the importance of MTHFR, methylation, and how to treat most effectively
- Inform the health insurance industry of the importance of MTHFR testing and the use of nutrients necessary to realize improvement

Action List

CASE STUDY CLIPS

MTHFR in Real Life – My own methylation data

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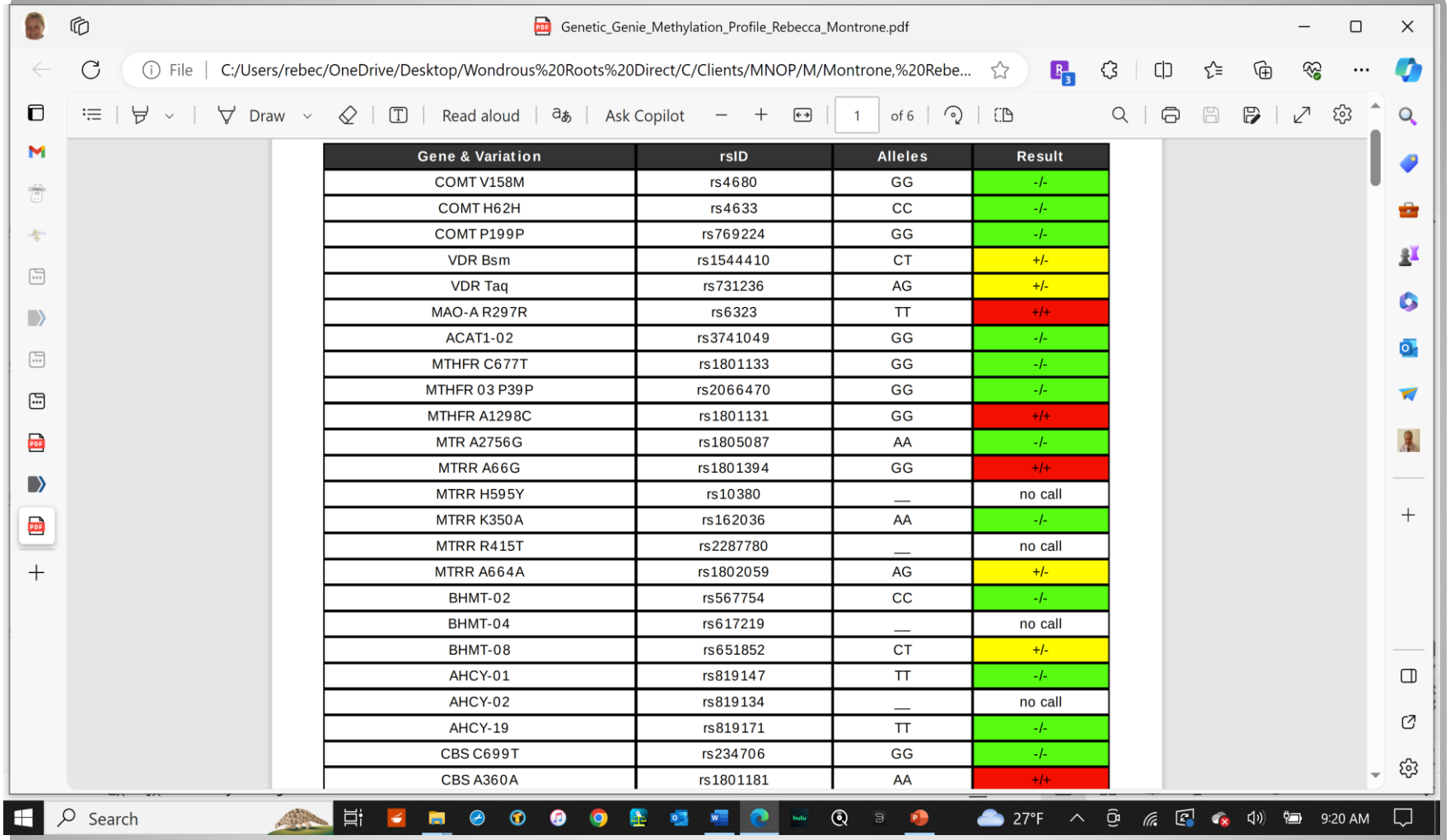

Gene & Variation	rsID	Alleles	Result
COMT V158M	rs4680	GG	-/-
COMT H62H	rs4633	CC	-/-
COMT P199P	rs769224	GG	-/-
VDR Bsm	rs1544410	CT	+/-
VDR Taq	rs731236	AG	+/-
MAO-A R297R	rs6323	TT	+/+
ACAT1-02	rs3741049	GG	-/-
MTHFR C677T	rs1801133	GG	-/-
MTHFR 03 P39P	rs2066470	GG	-/-
MTHFR A1298C	rs1801131	GG	+/+
MTR A2756G	rs1805087	AA	-/-
MTRR A66G	rs1801394	GG	+/+
MTRR H595Y	rs10380	__	no call
MTRR K350A	rs162036	AA	-/-
MTRR R415T	rs2287780	__	no call
MTRR A664A	rs1802059	AG	+/-
BHMT-02	rs567754	CC	-/-
BHMT-04	rs617219	__	no call
BHMT-08	rs651852	CT	+/-
AHCY-01	rs819147	TT	-/-
AHCY-02	rs819134	__	no call
AHCY-19	rs819171	TT	-/-
CBS C699T	rs234706	GG	-/-
CBS A360A	rs1801181	AA	+/+

My methylation data

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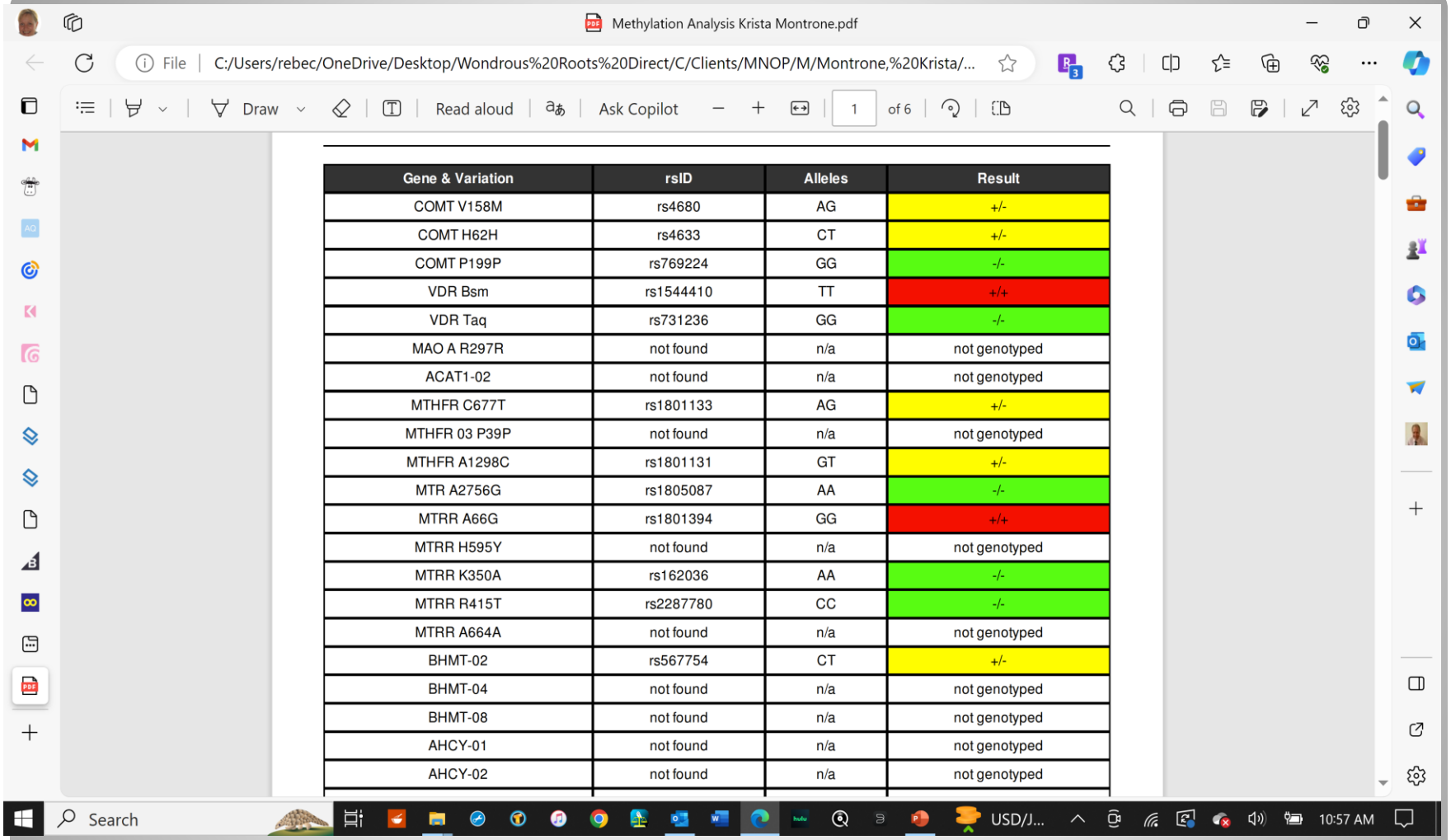

Gene & Variation	rsID	Alleles	Result
COMT V158M	rs4680	AG	+/-
COMT H62H	rs4633	CT	+/-
COMT P199P	rs769224	GG	-/-
VDR Bsm	rs1544410	TT	+/+
VDR Taq	rs731236	GG	-/-
MAO A R297R	not found	n/a	not genotyped
ACAT1-02	not found	n/a	not genotyped
MTHFR C677T	rs1801133	AG	+/-
MTHFR 03 P39P	not found	n/a	not genotyped
MTHFR A1298C	rs1801131	GT	+/-
MTR A2756G	rs1805087	AA	-/-
MTRR A66G	rs1801394	GG	+/+
MTRR H595Y	not found	n/a	not genotyped
MTRR K350A	rs162036	AA	-/-
MTRR R415T	rs2287780	CC	-/-
MTRR A664A	not found	n/a	not genotyped
BHMT-02	rs567754	CT	+/-
BHMT-04	not found	n/a	not genotyped
BHMT-08	not found	n/a	not genotyped
AHCY-01	not found	n/a	not genotyped
AHCY-02	not found	n/a	not genotyped

My daughter's methylation data

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