# The ABC’s of MTHFR and COMT: Bridging the Practice Gap

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# Disclosures

none

# Objectives

1. understand the significance of MTHFR and COMT clinical presentations
2. Learn how personalized nutrition, supplements, and lifestyle changes improve sleep and overall health.
3. Recognize the emotional and psychological impacts of chronic health issues and how functional medicine empowers patients.
4. Highlight the practice gap in clinical application of MTHFR and COMT

# Case Introduction - A Life of Anxiety, Depression, and Exhaustion

- Meet our patient: Maddie
- Struggled with anxiety and depression since childhood.
- Known for intense focus and discipline in school and athletics.
- Experienced cycles of energy crashes and feelings of being overwhelmed.
- Exhaustion upon waking, despite long hours in bed.
- Vivid, tiring dreams made her feel unrested.
- Aversive to processed foods due to brain fog and fatigue.

# The Emotional Impact on Maddie’s Identity

- Labeled as the "sick girl" throughout her life.
- Shamed for avoiding certain foods, accused of having an eating disorder.
- Carried guilt and shame for her health struggles.
- Anxiety around her health worsened her overall wellbeing.

# Searching for Answers in Conventional Healthcare

- Treated symptomatically with minimal improvement.
- Struggled with lack of comprehensive care addressing the root cause.
- Focus on anxiety, depression, and sleep as isolated issues.
- No lasting relief despite medication and counseling.

# Turning Point – Seeking Functional Medicine

- Consulted a functional medicine doctor who explored root causes.
- Underwent comprehensive genetic testing and lifestyle assessments.
- Discovered polymorphisms in **MTHFR** and **COMT (Val158Met)**.

# What we have learned

1980 23 chromosomes

1990 identified 10,000 base pairs

2000 identified 24,000 base pairs

2024 identified 3,079,843,747 base pairs

200,000 metabolic pathways

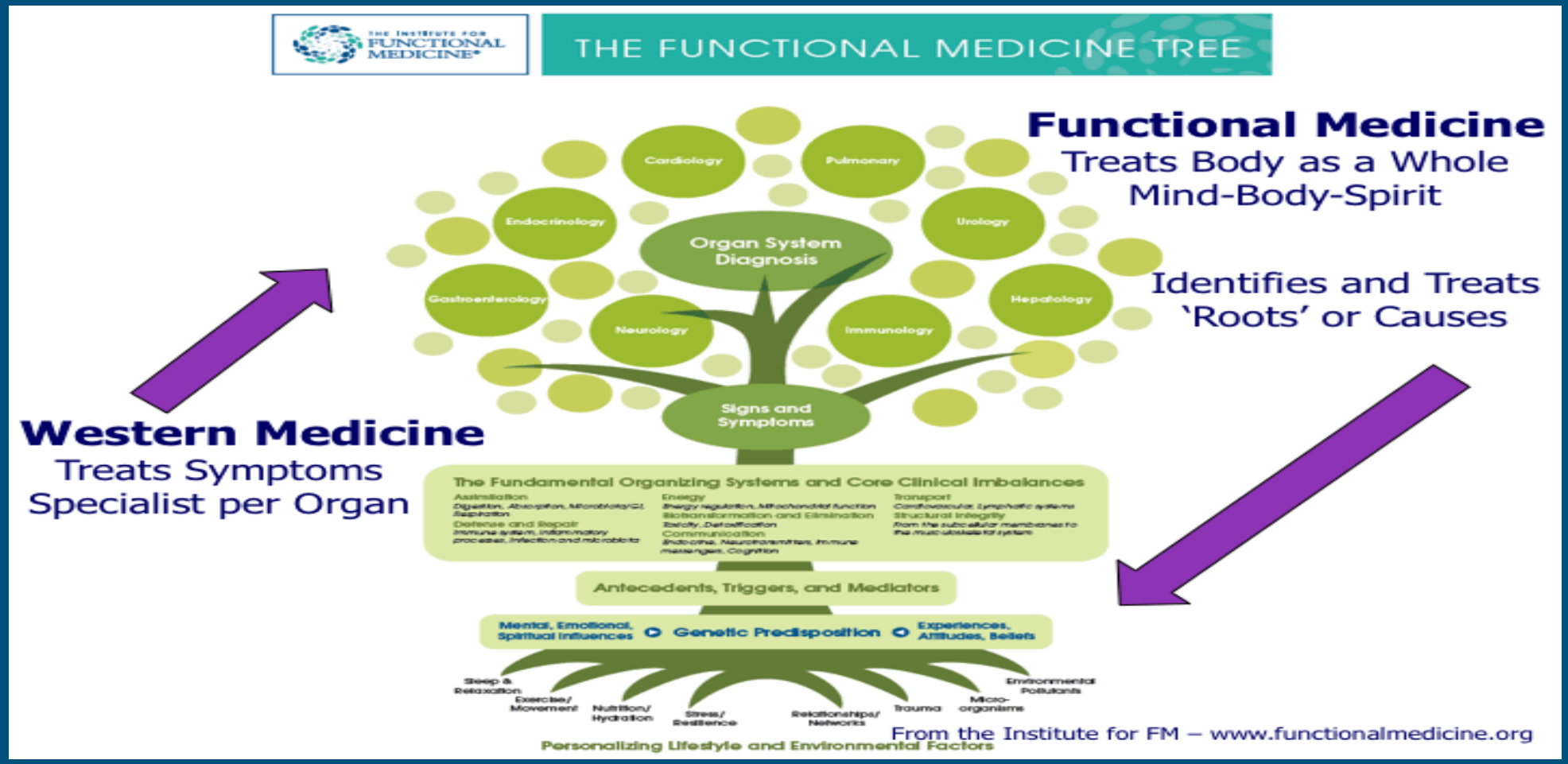
# Storyline Approach to Systems Biology

**Weaving the Story**:

- Each patient presents with a unique history, and by mapping their journey through the **Timeline and AMT**, we address their health systemically.
- Explore **key clinical nodes**: Assimilation, Defense & Repair, Energy, Biotransformation, Transport, Communication, Structural Integrity, Mental, Emotional, and Spiritual health.

# How did we get there

Breaking down the steps of functional medicine



# Introduction to Functional Medicine

- **Overview of Functional Medicine**
  - Personalized, patient-centered approach
  - Focus on root cause resolution
  - Systems biology perspective: Understanding the interconnectedness of body systems
- **The Functional Medicine Timeline**
  - Timeline: Uncovering patient history
  - **AMT (Antecedents, Mediators, Triggers)** framework: Addressing factors contributing to disease

# The Functional Medicine Systems Biology Framework

- **The 7 Core Nodes of Health**
  - **Assimilation** (Digestion/Absorption, Microbiota, Respiration)
  - **Defense & Repair** (Immune, Inflammation, Infection/Microbiota)
  - **Energy** (Energy Regulation/Mitochondrial Function)
  - **Biotransformation & Elimination** (Detoxification)
  - **Transport** (Cardiovascular/Lymphatic Systems)
  - **Communication** (Endocrine, Hormones, Neurotransmitters)
  - **Structural Integrity** (From Cellular to Musculoskeletal Structure)

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# Functional Medicine Matrix

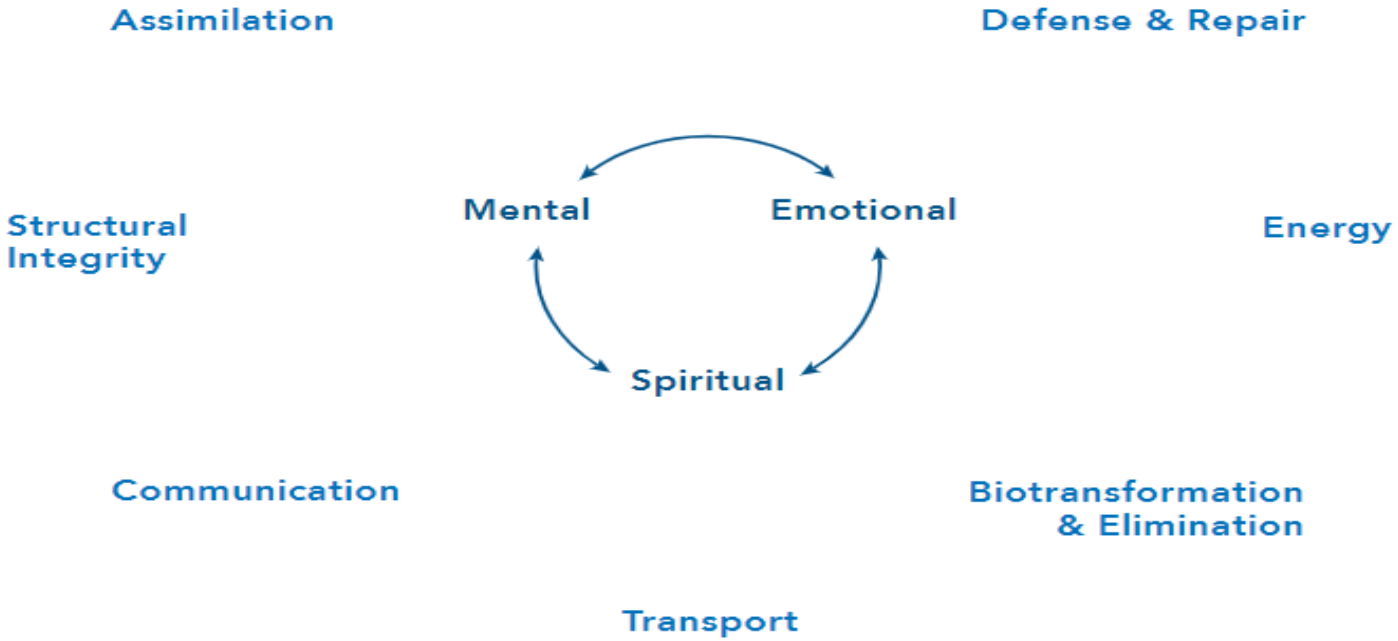
## Retelling the Patient's Story

**Antecedents**

**Triggering Events**

**Mediators/Perpetuators**

## Physiology and Function: Organizing the Patient's Clinical Imbalances




## Modifiable Personal Lifestyle Factors

| Sleep & Relaxation | Exercise & Movement | Nutrition | Stress | Relationships |
|---|---|---|---|---|
| | | | | |

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# Putting the pieces together

- Putting systems biology into clinical application using Functional Medicine
- By shifting the traditional disease-centered focus of medical practice to a more patient-centered approach, Functional Medicine addresses the whole person, not just an isolated set of symptoms

**Disease is an endpoint and symptoms are the signs of the disease**

# ALLOSTATIC LOAD

Guidi J, Lucente M, Sonino N, Fava GA. **Allostatic Load and Its Impact on Health: A Systematic Review.** Psychother Psychosom. 2021;90(1):11-27. doi: 10.1159/000510696. Epub 2020 Aug 14. PMID: 32799204.

Allostatic load refers to the cumulative burden of chronic stress and life events. It involves the interaction of different physiological systems at varying degrees of activity. When environmental challenges exceed the individual ability to cope, then allostatic overload ensues. Allostatic load is identified by the use of biomarkers and clinical criteria.

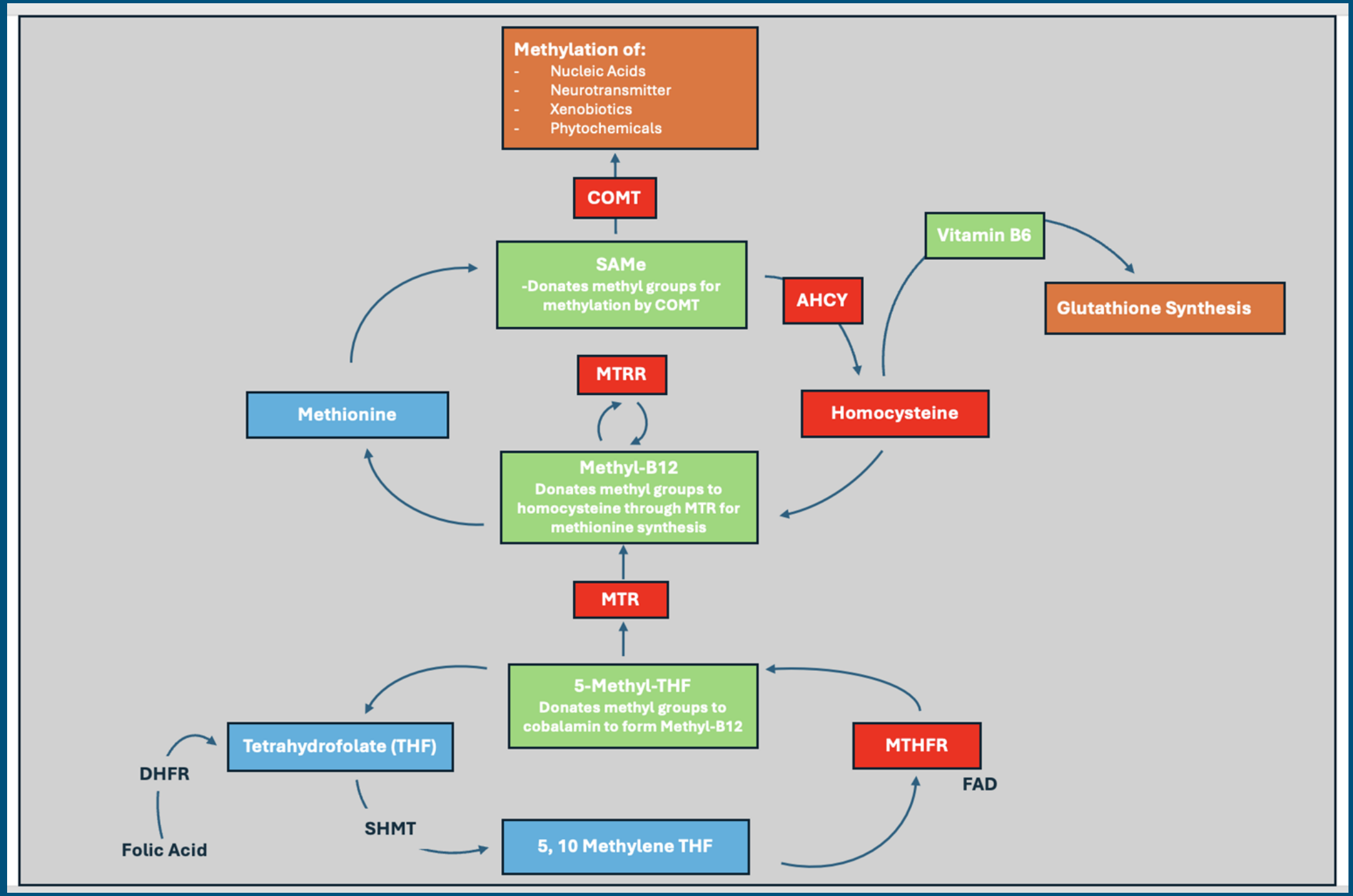
The findings indicate that allostatic load and overload are associated with poorer health outcomes. Assessment of allostatic load provides support to the understanding of psychosocial determinants of health and lifestyle medicine. An integrated approach that includes both biological markers and clinimetric criteria is recommended.

# MTHFR & COMT – A Key Discovery

- **MTHFR**: Affects folate metabolism, linked to mood and energy levels.
- **COMT (Val158Met)**: Impacts dopamine metabolism, contributing to Maddie's high focus and energy bursts, but also crashes.
- Helped her understand her genetic predisposition and how it affected her anxiety, sleep, and mood.

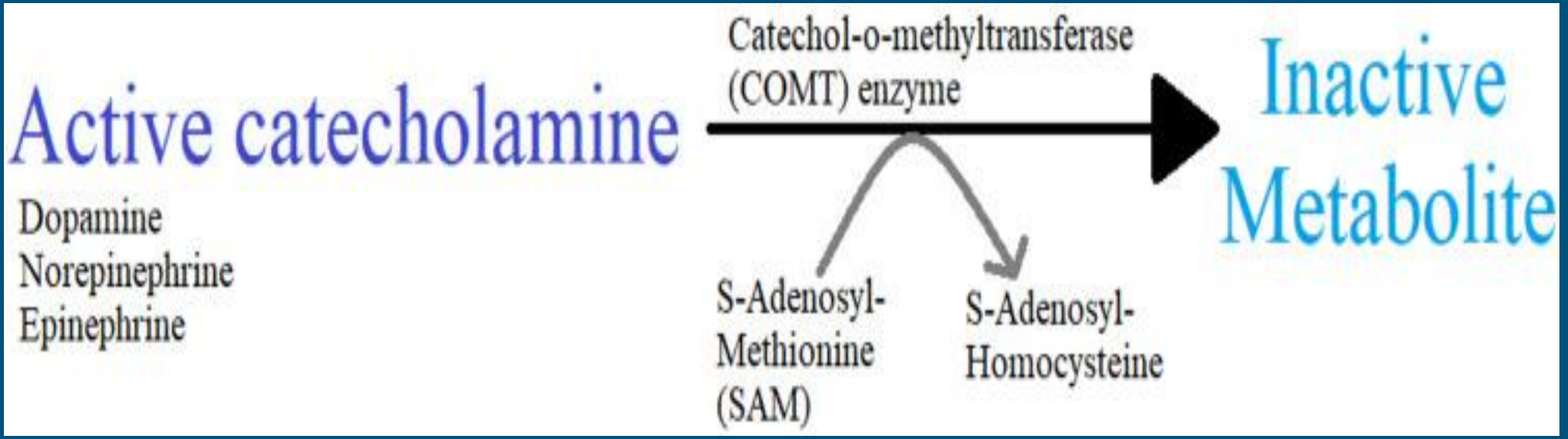
- Catechol-*O*-Methyltransferase gene *val*158*met* polymorphism and depressive symptoms during early childhood

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5288403/


Methylation of:
- Nucleic Acids
- Neurotransmitter
- Xenobiotics
- Phytochemicals
COMT
SAMe
-Donates methyl groups for methylation by COMT
AHCY
Vitamin B6
Glutathione Synthesis
MTRR
Methionine
Homocysteine
Methyl-B12
Donates methyl groups to homocysteine through MTR for methionine synthesis
MTR
5-Methyl-THF
Donates methyl groups to cobalamin to form Methyl-B12
Tetrahydrofolate (THF)
DHFR
Folic Acid
SHMT
5, 10 Methylene THF
MTHFR
FAD

# COMT

Catechol-O-methyltransferase (COMT) is an enzyme that catalyzes the methylation of catechol substrates during the metabolism of catecholamines (mainly norepinephrine and epinephrine) within the body




https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8553290/

# COMT and SLEEP

- Catechol-O-methyltransferase, dopamine, and sleep-wake regulation
- Current heritability estimates of sleep phenotypes vary between 20 and 40% for habitual sleep duration, to over 90% for the spectral characteristics of the electroencephalography (EEG) in non-rapid eye movement (REM) sleep
- https://doi.org/10.1016/j.smrv.2014.10.006

# COMT Stats

The COMT Val158Met (rs4680) is a common mutation in the catechol-O-methyltransferase (COMT) gene that can reduce enzymatic activity and increase dopamine levels.

The COMT gene is located on chromosome 22q11 and encodes the COMT protein, which breaks down dopamine and norepinephrine.

- White participants: 25% Met/Met, 51% Met/Val, and 24% Val/Val
- Black participants: 10% Met/Met, 44% Met/Val, and 46% Val/Val

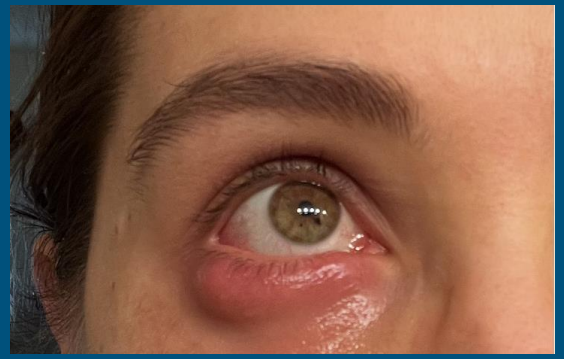
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6162781/#:~:text=3.1.-,1.,0.60).

# Assimilation (Digestion, Absorption, Microbiota, Respiration)

- **Antecedents**:
  - Genetic predispositions (e.g., MTHFR, COMT)
    - Our case: MTHFR 677CT, COMT MET/MET
- **Triggers**:
  - Nutrition/diet, infections, environmental toxins, Folate additives
    - Our case: folic acid in multivitamin and daily foods; antibiotics, travel abroad, COVID
- **Mediators**:
  - Chronic inflammation, gut dysbiosis, stress
    - Our case: diagnosed with IBS
- **Interventions**:
  - Restore gut function via 5R approach (Remove, Replace, Reinoculate, Repair, Rebalance)
  - Support respiration through proper breathing techniques and respiratory health.

# Defense & Repair (Immune Function, Inflammation, Infection)

- **Antecedents**:
  - Family history of autoimmune diseases
    - Our case: Father with Lichen planus, sister with Thalassemia
- **Triggers**:
  - Exposure to pathogens, poor diet, stress
    - Our case: Mold in house, restrictive diet, intense exercise, medical school
- **Mediators**:
  - Chronic infection, inflammation, dysregulated immune response
    - Our case: Rash on torso for months, chronic eye infections
- **Interventions**:
  - Anti-inflammatory diet, immune-modulating botanicals, probiotics to restore microbiome balance



# Energy (Mitochondrial Function)

- **Antecedents**:
  - Genetic factors affecting mitochondrial function
- **Triggers**:
  - Toxin exposure, chronic stress, nutrient deficiencies
- **Mediators**:
  - Oxidative stress, mitochondrial dysfunction
- **Interventions**:
  - Nutritional support (CoQ10, B vitamins, magnesium), antioxidant therapy, energy-restoring activities (exercise, proper sleep)

# Maddie

- Removed all folic acid from diet (supplements, manufactured goods)
- Methylated B12 supplement
- Still in medical school, so couldn’t eliminate that stressor
  - had to focus on other things
  - functional medicine doesn’t ask you to put your life on hold, but looks for tangible and realistic components of one’s life to tweak
- Discussions with family
  - support and understanding is crucial
- Minor changes in exercise routine
- Sleep hygiene
  - notice we aren’t only focusing on sleep to treat her sleep/energy disorders

# Biotransformation & Elimination (Toxicity/Detoxification)

- **Antecedents**:
  - Family history of detoxification issues (e.g., slow liver metabolism)
- **Triggers**:
  - Exposure to environmental toxins, heavy metals, poor diet
- **Mediators**:
  - Impaired detox pathways, overburdened liver function
- **Interventions**:
  - Support liver function with antioxidants (NAC, Glutathione), eliminate environmental toxins, improve gut health for elimination

# Transport (Cardiovascular/Lymphatic Systems)

- **Antecedents**:
  - Genetic predisposition to cardiovascular disease, poor lymphatic drainage
- **Triggers**:
  - Sedentary lifestyle, poor diet, stress
- **Mediators**:
  - Vascular inflammation, poor circulation, lymphatic congestion
- **Interventions**:
  - Cardiovascular support (omega-3s, anti-inflammatory diet), improve lymphatic flow (dry brushing, movement)

# Communication (Endocrine, Hormones, Neurotransmitters)

- **Antecedents**:
  - Family history of endocrine issues (thyroid, adrenal disorders)
- **Triggers**:
  - Hormonal imbalance (e.g., menopause, andropause), chronic stress, poor diet
- **Mediators**:
  - Dysregulated hormones (e.g., cortisol, insulin), neurotransmitter imbalances
- **Interventions**:
  - Hormone balancing therapies (e.g., adaptogens, bioidentical hormones), stress management

# Structural Integrity (Cellular to Musculoskeletal Structure)

- **Antecedents**:
  - Genetic predisposition to joint issues, past injuries
- **Triggers**:
  - Poor posture, chronic stress, lack of physical activity
- **Mediators**:
  - Tissue damage, musculoskeletal imbalances
- **Interventions**:
  - Structural support (exercise, OMM, chiropractic care), optimize cellular health through nutrient support (collagen, bone health supplements)

# A New Approach to Health

- Customized nutrition plan based on her genetics (MTHFR variant).
- Introduced targeted supplements to support detox pathways.
- Addressed stress through mindfulness and lifestyle modifications.
- Focused on the **root cause** of her sleep disorder, not just the symptoms.

# Maddie’s Transformation After Functional Medicine

- Reduced brain fog and fatigue with a clean, whole-foods diet.
- Improved ability to fall asleep and stay asleep.
- Vivid dreams reduced; waking up feeling refreshed.
- Shifted from feeling "sick" to empowered by understanding her genetic strengths.

# Empowered by Genetic Knowledge

- Learned how to use her **COMT variant** to harness extended focus.
- No longer viewed her health challenges as personal failings.
- Empowered to manage her health with the right tools and lifestyle changes.

# Why Functional Medicine Works for Sleep Disorders

- Sleep disorders are not isolated—they involve the whole body.
- Personalized care based on genetics, lifestyle, nutrition, and mental health.
- Focus on **root causes**, not just symptoms.
- Improved sleep by improving overall health and wellness.

# Sleep is More Than Sleep, it can be a clue to health or lack thereof

- Sleep problems often stem from complex health issues.
- Functional medicine treats the person as a whole, addressing underlying causes.
- Maddie’s story is a testament to the life-changing potential of this approach.

# Functional Medicine N=1

**UNITY**

**STRENGTH**

**PRECISION**