MTHFD1 Double Homozygosity (rs2236225, rs1076991)

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Genomic Architecture and Molecular Pathophysiology

Methylenetetrahydrofolate dehydrogenase 1 (MTHFD1), encoded by the *MTHFD1* gene located on chromosome 14q24, is a pivotal trifunctional enzyme in cytosolic one-carbon metabolism. The enzyme catalyzes three sequential, interconnected reactions: 5,10-methylenetetrahydrofolate dehydrogenase, 5,10-methenyltetrahydrofolate cyclohydrolase, and 10-formyltetrahydrofolate synthetase. These enzymatic steps regulate the interconversion of tetrahydrofolate (THF) derivatives required for *de novo* purine nucleotide synthesis, thymidylate (dTMP) production, and the generation of 5-methyltetrahydrofolate (5-MTHF), which donates methyl groups for the remethylation of toxic homocysteine into methionine.

Double homozygosity across two critical *MTHFD1* single-nucleotide polymorphisms—rs2236225 (c.1958G>A; R653Q) and rs1076991 (C>T)—establishes a profound, compound genetic bottleneck. The rs2236225 A allele alters the synthetase domain of the enzyme, compromising thermostability and impairing *de novo* purine synthesis (Carroll et al., 2009). Concurrently, the rs1076991 T allele resides within the promoter region and reduces transcriptional initiation, causing up to a 70% decrease in overall *MTHFD1* gene expression (Carroll et al., 2009; Ding et al., 2016).

When a patient is double homozygous (rs2236225 AA and rs1076991 TT), the combination of severely diminished gene transcription and structural instability of the residual protein creates a severe biological deficit. This dual defect disrupts both cellular nucleotide synthesis and homocysteine clearance pathways. The resulting accumulation of homocysteine, paired with depleted cellular methylation potential, initiates microvascular damage, genomic instability, and systemic hypercoagulability.

Cardiovascular Manifestations and Systemic Disease Risks

The primary cardiovascular consequence of MTHFD1 double homozygosity is hyperhomocysteinemia-mediated endothelial destruction and atherothrombosis. Elevated circulating homocysteine generates reactive oxygen species, downregulates endothelial nitric oxide synthase, and triggers systemic endothelial inflammation. Clinical studies establish that functional *MTHFD1* variants significantly alter plasma amino acid kinetics (glycine and serine interconversion) and double the relative hazard of acute myocardial infarction (AMI) and coronary artery disease progression (Ding et

al., 2016). Microvascular thrombosis, accelerated coronary atherosclerosis, and arterial stiffness are prominent physical manifestations in these patients.

Beyond macrovascular disease, **MTHFD1 double homozygosity severely impacts reproductive health and embryogenesis.** Impaired 10-formyl-THF and 5,10-methylene-THF synthesis starves rapidly dividing fetal and placental cells of purines and pyrimidines. Maternal carrying of the rs2236225 and rs1076991 variants strongly correlates with recurrent pregnancy loss (RPL), intervillous placental thrombosis, early miscarriage, and placental insufficiency (Pjetri & Zeisel, 2017). Furthermore, maternal double homozygosity elevates the risk of birth defects in offspring, particularly neural tube defects (NTDs) such as spina bifida and congenital heart defects (CHD), including Tetralogy of Fallot (Karas Kuželički et al., 2022; Song et al., 2022).

At the systemic level, **severe MTHFD1 enzyme impairment leads to megaloblastic anemia secondary to defective nuclear thymidylate synthesis, causing uracil misincorporation into DNA and chromosome strand breaks.** Because the folate-dependent methyl cycle is compromised, patients exhibit extreme vulnerability to dietary choline depletion—demonstrating up to a **15-fold higher likelihood of developing choline-deficiency organ dysfunction (hepatic steatosis and muscle breakdown) when choline intake is low (Pjetri & Zeisel, 2017). Central nervous system manifestations include an increased susceptibility to mood disorders, attentional deficits, and neurodevelopmental conditions due to reduced S-adenosylmethionine (SAMe) availability for neurotransmitter synthesis.**

(Causes Tourette's)

Conventional Pharmacotherapy, Biologicals, and Clinical Trade-offs

Managing patients with MTHFD1 double homozygosity requires suppressing hyperhomocysteinemia, bypassing metabolic bottlenecks, and protecting against secondary thrombotic events.

Therapy / Intervention	**Drug Class & Mechanism**	**Clinical Effectiveness**	**Key Side Effects & Clinical Trade-offs**
Low-Dose Aspirin (81 mg/day)	Antiplatelet / Cyclooxygenase-1 (COX-1) inhibitor; suppresses thromboxane A2 aggregation.	High in primary and secondary prevention of arterial thrombosis and pregnancy loss.	Dyspepsia, gastric mucosal ulceration, GI bleeding, patient refusal due to bleeding fears.

Therapy / Intervention	Drug Class & Mechanism	Clinical Effectiveness	Key Side Effects & Clinical Trade-offs
Source Naturals Mega-Folinic Acid (5-formyl-THF)	Active Bioavailable Folate; directly bypasses the MTHFD1 synthetase block for nucleotide synthesis.	Superior efficacy in restoring purine/dTMP pools and reducing megaloblastic anemia.	Well tolerated; high doses without B12 monitoring may mask underlying B12 deficiency.
Betaine (Trimethylglycine / TMG)	Alternative Methyl Donor; activates the hepatic BHMT pathway to clear homocysteine.	High efficacy as a non-folate-dependent backup remethylation pathway.	Mild GI upset, fishy body odor at extremely high doses (rare at standard dosing).
Direct Oral Anticoagulants (DOACs)	Factor Xa / Direct Thrombin Inhibitors (e.g., Apixaban, Rivaroxaban).	Recommended only for acute secondary venous thromboembolism (VTE) prevention.	Major bleeding risk, hematoma, high financial cost ($350–$600/month).

Standard medical guidelines frequently center on daily low-dose baby aspirin as preventive therapy to counter endothelial platelet activation. However, aspirin does not correct the underlying metabolic deficit in one-carbon metabolism, nor does it lower homocysteine. Furthermore, many patients refuse daily aspirin therapy due to chronic gastrointestinal intolerance, bleeding risks, or a strict preference for non-pharmaceutical protocols.

Stand-Alone Natural Protocols for Aspirin-Refusive Patients

For patients with MTHFD1 double homozygosity who refuse daily baby aspirin and seek stand-alone natural protocols, therapeutic management must simultaneously achieve two objectives: metabolic bypass of the enzyme bottleneck and non-pharmaceutical antithrombotic protection.

1. Dual-Pathway Methylation Bypass (BHMT & Direct Folate Routing)

Because MTHFD1 double homozygosity impairs the conversion of THF to 5,10-methylene-THF, the body's dependence on the alternative betaine-homocysteine

methyltransferase (BHMT) pathway increases exponentially (Pjetri & Zeisel, 2017). A stand-alone nutritional bypass utilizes high-dose **Phosphatidylcholine** (or CDP-Choline) combined with **Betaine (TMG)**. Betaine donates methyl groups directly to homocysteine in the liver and kidneys independently of folate or vitamin B12. Concurrently, supplementing with **Folinic Acid (5-formyl-THF)** supplies the immediate form required for purine and pyrimidine synthesis, while **Pyridoxal-5-Phosphate (Active B6)**, and **Methylcobalamin (B12)** rapidly clear systemic homocysteine, eliminating the vascular toxin at its source.

2. Natural Fibrinolytic and Antiplatelet Protection

To replace the antiplatelet coverage of baby aspirin, natural systemic fibrinolytic enzymes—specifically **Kindernyl Nattokinase** (10,000 FU daily) — is utilized. Nattokinase directly degrades intravascular fibrin mesh and cleaves active PAI-1, inhibiting spontaneous microthrombus formation without inducing gastric mucosal toxicity.

Combining systemic enzymes with high-dose **Omega-3 Fatty Acids (EPA/DHA) (this is the best in the USA – DFH OmegaVail Synergy -- https://www.designsforhealth.com/products/omegavail-synergy#OVS060) and Curcumin (only validated one in the world is in this product which I take – Resveratrol Supreme -- https://www.designsforhealth.com/products/resveratrol-supreme#RVS060)** inhibits COX-1/COX-2 pathways and downregulates NF-κB-driven endothelial cell adhesion molecules (ICAM-1, VCAM-1), matching aspirin's anti-inflammatory and anti-thrombotic properties.

3. Intracellular Redox Preservation (The VARS Triad)

Hyperhomocysteinemia triggers severe mitochondrial oxidative stress, generating superoxide free radicals that destroy endothelial nitric oxide. The VARS Triad—comprising Validated, Absorbable, Reduced, and Stable formulations of VARS **Glutathione**, VARS **Superoxide Dismutase (SOD)**, and VARS **Catalase (all three either patented biologics and/or patent pending)** —serves as an intracellular redox shield. SOD converts superoxide into hydrogen peroxide, which Catalase breaks down into water and oxygen, while reduced Glutathione quenches residual peroxides. By eliminating intracellular ROS, the VARS Triad halts endothelial apoptosis and prevents the pro-inflammatory signaling that accelerates thrombosis in MTHFD1-deficient patients.

References

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