The COMT–Mitochondrial Connection

Why SS-31 and Rapamycin Work So Exceptionally Well — A Genetic and Biochemical Explanation

Part 1: The COMT Variant and Lifelong ADD

You carry a heterozygous COMT variant (rs4680, A/G), meaning your COMT enzyme — responsible for breaking down dopamine in the prefrontal cortex — runs slower than normal. This is one of the most well-studied genetic variants in psychiatry and neuroscience, and it creates a very specific pattern of cognitive challenge.

The key distinction is that your ADD stems from **dopamine dysregulation**, not dopamine deficiency. The prefrontal cortex operates on an inverted-U curve — too little dopamine AND too much dopamine both impair executive function. Slow COMT creates instability in this system, making it difficult to filter distractions and maintain consistent attention.

When you briefly tried low-dose Adderall, it felt clarifying rather than stimulating — a characteristic signature of the slow COMT variant, where dopamine was being nudged into an optimal range rather than overshooting it.

You correctly stopped Adderall due to your cardiovascular history — a decision fully supported by your genetic profile, which includes homozygous 9p21 myocardial infarction risk variants (x4), PHACTR1 and ADR-B2 thromboembolism variants, and an ACE D/D variant.

Part 2: The Missing Link — Mitochondrial Dysfunction

The prefrontal cortex is the most energy-hungry region of the brain, and COMT itself is an energy-dependent enzyme that requires adequate ATP to function. This creates a critical vulnerability when mitochondrial function is impaired:

- Mitochondrial dysfunction → reduced ATP production
- Reduced ATP → COMT activity slows further (beyond the genetic baseline)
- Slower COMT → dopamine regulation in the prefrontal cortex deteriorates
- Deteriorated dopamine regulation → ADD symptoms worsen significantly

Micronutrient testing confirmed **significant CoQ10 deficiency on both serum and cellular measures** (serum: 0.23, reference 0.56-2.78; cellular WBC: 32.1, reference 39.6-225.3) — the missing link explaining why the COMT variant progressed from a genetic vulnerability into clinically significant

symptoms.

A GPX1 variant (rs1050450, heterozygous C/T) also reduces glutathione peroxidase activity, increasing oxidative stress and further impairing mitochondrial efficiency. The genetic vulnerability and mitochondrial dysfunction were compounding each other.

Part 3: Why SS-31 (Elamipretide) Works So Exceptionally Well

SS-31 works by stabilizing cardiolipin on the inner mitochondrial membrane, directly restoring electron transport chain efficiency and ATP production. For most people this primarily means improved energy and reduced fatigue. For you, the effect goes much deeper:

> *Restoring mitochondrial ATP production gives your COMT enzyme the energy substrate it needs to regulate prefrontal cortex dopamine properly — addressing the root cause of your ADD rather than pharmacologically overriding it.*

The results have been dramatic — complete elimination of ADD symptoms and significant fatigue resolution on SS-31, with symptoms returning on days the injection is missed. This dose-response relationship strongly supports a real mechanistic effect rather than placebo.

The day-to-day variability in cognitive function maps precisely to the SS-31 dosing schedule. On days without the injection, mitochondrial protection wanes, ATP availability drops, COMT function deteriorates, and prefrontal dopamine regulation becomes less stable. More consistent daily dosing would likely produce more consistent cognitive function, though every-other-day dosing may capture the majority of benefit given SS-31's half-life kinetics of approximately 2-4 hours.

Part 4: Why Rapamycin Resolved Lifelong Insomnia

Lifelong insomnia resolved completely upon starting rapamycin — and there is a compelling mechanistic explanation connecting mTOR signaling, circadian rhythm, and the COMT variant.

The mTOR-orexin connection: mTOR signaling is temporally controlled by the circadian clock. When mTOR is chronically overactive it upregulates orexin production — the primary wakefulness neurotransmitter. Excess orexin keeps the brain hyperaroused at night, making it extremely difficult to fall and stay asleep. Research confirms that sleep abnormalities and increased orexin expression are reversed by rapamycin treatment, indicating direct mTOR dependence.

The COMT-norepinephrine connection: Your COMT slow variant also means slower clearance of norepinephrine — a wakefulness-promoting catecholamine. Slower norepinephrine clearance keeps the brain more activated at night, adding a second independent mechanism driving insomnia — present from birth, explaining why the insomnia was lifelong.

- **Driver 1:** Overactive mTOR → excess orexin → hyperarousal at night
- **Driver 2:** Slow COMT → slow norepinephrine clearance → brain not quieting down

Rapamycin suppressed mTOR → normalized orexin → removed Driver 1. SS-31 restoring COMT function → better norepinephrine clearance → removed Driver 2. Together they eliminated both mechanisms of lifelong insomnia simultaneously.

The resolution was complete because both root causes were addressed directly. Additionally, rapamycin's neuroprotective effects help mitigate cognitive damage accumulated from decades of poor sleep — particularly relevant given APOE4 status.

Part 5: The Complete Picture

Two interventions — SS-31 and rapamycin — are simultaneously addressing multiple converging genetic and biochemical vulnerabilities through root-cause mechanisms:

Intervention	Mechanism	Outcome
SS-31	Stabilizes cardiolipin → restores mitochondrial ATP	ADD resolved, fatigue resolved, COMT normalized
SS-31	Cardiac mitochondrial membrane protection	Cardiovascular-safe alternative to stimulants
Rapamycin	mTOR inhibition → normalizes orexin	Lifelong insomnia resolved completely
Rapamycin	Autophagy → clears damaged mitochondria	Synergistic with SS-31 for mitochondrial health
Rapamycin	Neuroprotection from sleep deprivation damage	Critical given APOE4 status

This represents an unusually clear example of a genetically-mediated mitochondrial-neurotransmitter interaction, where targeted interventions address root causes rather than masking symptoms — and do so through mechanisms that are safe for a high cardiovascular risk profile.

Relevant Genetic Variants Referenced

Gene	Variant	Genotype	Relevance
COMT	rs4680	A/G heterozygous	Slow dopamine/norepinephrine clearance — ADD and lifelong insomnia
9p21 x4	Multiple	G/G homozygous	Elevated myocardial infarction and coronary artery disease risk
PHACTR1	rs169713	T/T homozygous	Elevated venous thromboembolism risk

ADR-B2	rs1042714	G/G homozygous	Elevated idiopathic thromboembolism risk
ACE	rs4646994	D/D homozygous	Elevated ACE activity — supports telmisartan rationale
APOE	ApoE	e3/e4	APOE4 — Alzheimer's and cardiovascular risk
MTHFR	rs1801131	A/C heterozygous	A1298C — homocysteine elevation, methylated B vitamins required
GPX1	rs1050450	C/T heterozygous	Reduced glutathione peroxidase — increased oxidative stress

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This document is intended for informational and discussion purposes only. All interventions described are under the supervision of a licensed medical provider. Genetic variants from Vibrant Wellness CardiaX panel (January 2025). Micronutrient data from Vibrant Wellness Micronutrients panel (January 2025).