Know Your Machinery

How your genetic blueprint shapes substance metabolism, and why that matters.

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A note before you begin. This guide discusses genetic and metabolic factors in addiction. That framing can be misread in two directions: as an excuse, or as a sentence. It is neither. It is also not medical advice about your medications. Nothing here should be used to change, stop, or adjust a prescription. Those conversations belong with the person who prescribed them.

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A note before we go deeper. Some of what follows may feel like overkill if your recovery lens has mostly been abstinence-based or faith-based. The goal isn't to excuse behaviour. It's to add the perspective that's been missing. Understanding the biology behind addiction doesn't erase responsibility; it sharpens the conversation. Looking at genetic and metabolic factors lets us move beyond shame and moralizing and start asking a harder question: why do certain behavioural patterns not only emerge, but ruthlessly persist? This isn't a conversion to pharmacogenomics. It's context, offered because understanding the biology is one of the fastest ways to loosen shame's grip.

Your Genetic Blueprint and Substance Metabolism

A Personal Reflection

The first time I heard about genetic predisposition in relation to addiction, I called bullshit. I refused to believe I was born with crossed wires, or that my biology might be quietly steering the ship. It sounded like an excuse, and worse, it suggested that something else might be in control.

That started to change when I looked at my own family. My father avoided alcohol for most of his life because two or three beers made him sick. My body processed alcohol differently, efficiently enough that I could drink to excess and do it again the next day, and the day after that, for years. That contrast was impossible to explain away.

Years later, I see it much differently. Understanding the biology of addiction didn't weaken my sense of agency. It sharpened it. It gave me tools, context, and a kind of compassion I hadn't been able to access before. With every piece of science I absorbed, shame loosened its hold.

Think of Your Enzymes Like Tools in a Toolbox

Every substance you've ever taken, legal or illegal, has to pass through your body's chemical toolbox before it leaves your system. Those tools are your metabolic enzymes, and your genetics determine how they're built.

Imagine opening that toolbox. For some people, every tool is fitted perfectly: sleek, efficient, purpose-built. For others, the wrench is oversized, the blade is stripped, and half the tools don't match the job. The result? A group of people can take the same dose of alcohol, opioids, or antidepressants and walk away with completely different outcomes. One buzzing, one sick, one feeling nothing at all.

This is where biology collides with behaviour. Some enzyme variants can make an active drug or metabolite build up; others can reduce exposure or prevent a prodrug from becoming active. But 'fast means weak' and 'slow means strong' is not a universal rule. It depends on the substance, the pathway, liver health, other medications, dose, and whether the enzyme activates or clears the drug. Biology tilts the table. It does not use one set of rules for every molecule.

> *Biology doesn't dictate your substance of choice, but it tilts the table.*

The Key Players: Enzymes That Process Substances

The liver is the body's main processing plant, and these enzymes are among its frontline workers. Genetic variation can help explain why two people process certain drugs differently, but dose, age, other medications, smoking, illness, kidney and liver function, and the drug's own chemistry often matter just as much or more.

CYP2D6 — breaks down many psychiatric medications, opioids, and stimulants.

— CYP2D6 is crucial for codeine because it converts codeine into morphine, and genotype can change both lack of effect and toxicity risk. It also contributes to the metabolism of many antidepressants and some stimulants. Fluoxetine is more complicated: it strongly inhibits CYP2D6 itself, and current CPIC guidance does not provide a genotype-based fluoxetine dosing recommendation.

CYP3A4 — metabolizes roughly half of all medications.

— CYP3A enzymes process alprazolam, fentanyl, and many other drugs. Enzyme activity varies enormously, but medications, grapefruit, smoking, illness, and liver function often matter more clinically than common CYP3A4 gene variants. CYP3A4 is not currently covered by a CPIC prescribing guideline.

CYP2C19 — processes SSRIs, proton pump inhibitors, and some benzodiazepines.

— CYP2C19 variation can affect exposure to citalopram, escitalopram, some proton-pump inhibitors, and certain other drugs. It can help guide prescribing for specific medication-gene pairs. It does not, by itself, explain why one person is sedated and another feels nothing.

ADH / ALDH2 — break down alcohol and its toxic byproducts.

— Reduced ALDH2 activity allows toxic acetaldehyde to accumulate, producing flushing, nausea, and a racing heart and generally lowering the risk of heavy drinking, even though drinking through the reaction raises cancer risk. ADH1B variants can also change how quickly acetaldehyde forms. 'Faster alcohol metabolism means more reward' is not a safe general rule.

COMT — clears dopamine and stress-related neurotransmitters.

— COMT variants influence dopamine breakdown in parts of the brain, but the effects are small, context-dependent, and inconsistent across complex behaviours. A COMT result cannot tell you that someone is a risk-taker, emotionally volatile, or destined to crave stimulation.

MAO-A — breaks down serotonin, dopamine, and norepinephrine.

— MAO-A helps metabolize monoamine neurotransmitters. Genetic effects on mood, aggression, or addiction are complex, small at the individual level, and shaped heavily by development and environment. A result is not a personality test.

CES1 — helps break down methylphenidate (Ritalin) and several other drugs.

— CES1 variation may contribute to differences in methylphenidate levels and side effects. It is one factor among many, not a complete explanation for why a dose feels overwhelming or ineffective.

UGTs — detoxify substances via glucuronidation, a non-CYP pathway.

— Lorazepam is cleared mainly through glucuronidation rather than oxidative CYP metabolism. That can matter in some liver conditions, but it does not make the drug automatically safe or well tolerated; liver disease, sedation, dependence risk, other medications, and dose still require clinical assessment.

> **A quick note on testing.** Pharmacogenomic panels can identify some gene-drug pairs with actionable prescribing guidance, especially for selected antidepressants, opioids, and other medications. They do not map your response to every medication, illicit drug, or alcohol, and they do not replace liver tests, medication review, or clinical history. Therapeutic drug monitoring can measure levels of certain prescriptions at specific times; it is not a live readout of your metabolism. Any decision belongs with a qualified prescriber or pharmacist.

At a Glance: Why "Fast" and "Slow" Aren't Enough

Enzyme activity can shape how hard some substances hit, how long they stay, and how much interaction risk accumulates. It is one part of drug response, not a master explanation for craving, tolerance, or substance preference. Receptors, learning, dose, route, health, other drugs, environment, and expectation all matter too.

CYP2D6

— When CYP2D6 clears an active drug, lower activity can raise exposure and side effects while higher activity can lower exposure. The actual effect depends on the medication.

— Prodrugs can run the other way. Codeine must be converted to morphine, so very low activity can mean little pain relief while ultrarapid activity can create dangerous morphine levels. Never adjust a dose from a generic fast/slow label.

ADH / ALDH2

— ADH enzymes help convert alcohol to acetaldehyde. ALDH2 helps clear acetaldehyde. Because they act at different steps, one fast/slow summary cannot predict reward, tolerance, or addiction.

— Reduced ALDH2 activity can cause flushing, nausea, and a rapid heartbeat. It often discourages heavy drinking, but drinking through the reaction raises cancer risk. It is not a harmless built-in brake.

COMT

— COMT variants can influence dopamine breakdown in parts of the brain, but effects on behaviour are small, context-dependent, and inconsistent.

— A COMT result cannot reliably tell you who will take risks, crave stimulation, react emotionally, develop addiction, or need a particular treatment.

> *Your genes don't dictate your choices, but they do shape the chemistry you're working with.*
>
> *Pharmacogenetics can sometimes narrow prescribing choices or explain an unusual response when a well-supported gene-drug pair exists. It cannot identify the one perfect medication from your blueprint. Use it as one piece of a clinical decision, not as a verdict.*

Beyond the Blueprint: How Chronic Use Rewires the System

Your genetic blueprint is the starting point, not the whole story. The substances you use, and the duration and intensity of that use, reshape these systems over time. Some of those changes reverse in recovery. This is one layer of the picture: important context, but not a complete explanation of addiction on its own.

Enzyme induction: the liver adapts to break down a drug faster. Clearance accelerates, tolerance builds, and the dose that once worked stops being enough.

Enzyme inhibition: some substances block the enzymes that process other drugs, causing unpredictable buildup and, in some cases, dangerous interactions.

Organ damage: chronic use can injure the liver, kidneys, or pancreas, eroding overall metabolic capacity and complicating medication dosing long after use stops.

Neuroadaptation: the brain adjusts to constant chemical exposure. Receptors downregulate or upregulate, neurotransmitter production shifts, and the ability to feel reward, from substances or from ordinary life, changes accordingly.

This is part of why two people with the same diagnosis can respond so differently to the same medication, and why history of use matters when treatment decisions get made.

What This Means for Future Treatment

Reduced medication effectiveness: altered receptors or metabolism can blunt the impact of antidepressants, pain medications, or mood stabilizers, making an otherwise appropriate prescription feel useless.

Higher risk of side effects: slowed clearance allows drugs to accumulate past therapeutic levels, into uncomfortable or toxic territory.

Greater risk of interactions: a taxed or over-adapted liver is easily overwhelmed when multiple medications compete for the same enzyme pathways.

More trial and error: unpredictable drug response means finding effective psychiatric or pain medications takes longer, and often costs more in failed attempts before something works.

When Treatment Becomes Template

Medication-assisted treatment can be life-saving. But too often it's applied like a template: the same medications handed to very different people, across very different histories, and measured against a standard that assumes everyone should respond roughly the same way.

The reality is that real metabolic differences exist from person to person, and years of substance use leave a mark on those processes in ways that aren't uniform. Alcohol, opiates, and stimulants don't just create different dependencies. They affect different systems in the body, and those systems are often the same ones medications need to work through. This is increasingly recognized in addiction medicine, even if the system isn't yet set up to routinely test for it.

Someone who spent years on alcohol arrives at treatment with a different internal landscape than someone coming off opiates or stimulants. Those differences matter when it comes to what medications are likely to help, what's likely to cause problems, and what the body simply won't respond to. But a doctor who actually knows your history, what you used, for how long, and what it did to you, can at least make an educated guess. That's not precision medicine. But it's a better starting point than the boilerplate.

> *A poor medication response does not automatically mean resistance, noncompliance, or lack of effort. Sometimes it means the treatment is too standardized for a system that was never standard to begin with.*

Before You Go

Understanding your genetics doesn't mean surrendering responsibility. It means you stop guessing. Your choices still matter, but they land differently when you know the ground you're standing on. Addiction is shaped by biology, environment, history, and circumstance. Reducing it to bad choices doesn't just miss the point. It fuels the shame that makes recovery harder.

The goal here isn't to send you chasing lab tests or genetic panels. It's to make clear that there are real, measurable mechanisms at work in your body, and that knowing this matters. Not because it changes what happened, but because it changes how you understand it.

One practical thing worth carrying out of this: if a medication hasn't worked for you, or has hit far harder than expected, that is information worth bringing to your prescriber along with an honest account of your use history. It is not evidence that you are treatment-resistant, and it is definitely not a reason to adjust anything on your own.

You are not broken for struggling. You are wired in a particular way, facing particular risks, and once you understand the system you're actually working with, the path forward gets a little less like guesswork and a little more like a plan.

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Sources & Further Reading

These sources cover the enzyme systems governing drug and alcohol metabolism, the genetic variants that shape them, and the clinical guidelines already using this information to reduce trial and error in prescribing.

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