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Joe Cohen - Combined Genetic Summary

Understanding your genetic profile as a whole

12	2	10	155
Total Genes	Disease Related Genes	LOF Genes	PRS Risk Traits

Important: This summary is for educational and informational purposes only. It is not intended to diagnose, treat, cure, or prevent any disease. Always consult with qualified healthcare providers for medical decisions.

IN THIS REPORT

Your Genetic Story

Your whole genome sequencing genetic analysis found rare variants that affect **how your body generates energy from fats and thyroid hormone production**. Understanding these helps you make better decisions about exercise, fasting, illness management, and when to seek medical attention.

Rare Variants Affecting Your Health

CPT2

The Carnitine Shuttle (getting long-chain fats into mitochondria)

CPT2 is part of your cells' "fat-to-energy" system.

With one pathogenic CPT2 variant (heterozygous carrier), many people feel completely well. That said, the reviewed literature shows that a small number of carriers can have 'classic' CPT2-type muscle symptoms—especially when they push their metabolism hard (endurance exercise, overheating/fever, or fasting). If symptoms happen, they tend to look like exercise-induced muscle pain/burning, cramps, weakness, or in rare cases rhabdomyolysis (muscle breakdown). The best way to think about it is: you likely have a safety margin most of the time, but your margin may shrink under stress.

DUOXA2

Thyroid hormone synthesis (the DUOX2/DUOXA2 "H2O2 spark" system)

DUOXA2 is like the "helper/escort" that gets DUOX2 to the right place in thyroid cells so it can make hydrogen peroxide (H2O2).

Being heterozygous (T/C) for a pathogenic DUOXA2 variant usually means you carry one working copy and one non-working (or less-working) copy. For many recessive thyroid dyshormonogenesis genes, carriers are often healthy because one working copy can be enough. That said, the DUOX system has a lot of real-world variability.

How You Process Medications

Your body processes certain medications differently than most people. This is important to know **before** you're prescribed these drugs.

CYP3A5

`*3/*3` Poor Metabolizer

Affected medications: Tacrolimus, Quetiapine (Seroquel®), Levomilnacipran (Fetzima®), Venlafaxine (Effexor®)

CYP3A5 is one of the enzymes that clears many medicines; people with *3/3* usually have little to no CYP3A5 function, which can raise levels of certain drugs. Tacrolimus is an immunosuppressant used to prevent organ transplant rejection and to treat some immune conditions; higher levels can increase risks like kidney problems, tremor, and high blood pressure. Quetiapine is a second-generation antipsychotic used for bipolar disorder, schizophrenia, and as an add-on for depression.

SLCO1B1

`*5/*37` Intermediate Function

Affected medications: Rosuvastatin, Atorvastatin, Fluvastatin, Lovastatin

SLCO1B1 helps move many statins from the blood into the liver (where they work). With intermediate function, some statins can reach higher blood levels, which increases the risk of muscle side effects (myopathy) and, rarely, severe muscle breakdown. Rosuvastatin, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, and simvastatin are "statins" (HMG-CoA reductase inhibitors) used to lower LDL cholesterol and reduce the risk of heart attack and stroke. Simvastatin/simvastatin acid and lovastatin/lovastatin acid refer to the active forms of those statins in the body.

VKORC1

`T/C` rs9923231 variant detected (altered response)

Affected medications: Warfarin, Acenocoumarol, Phenprocoumon

VKORC1 affects how sensitive your body is to vitamin K-antagonist blood thinners. Warfarin is an anticoagulant used to prevent or treat blood clots (such as deep vein thrombosis or pulmonary embolism) and to reduce stroke risk in atrial fibrillation or with certain heart valves. Acenocoumarol and phenprocoumon are similar anticoagulants used in some countries for the same clot-prevention purposes.

IFNL3

T/C | rs12979860 variant detected (altered response)

Affected medications: Triple therapy (peginterferon alfa-2a/b & ribavirin), interferons;peginterferon alfa-2a;peginterferon alfa-2b;ribavirin, peginterferon alfa-2a;peginterferon alfa-2b;ribavirin;telaprevir, peginterferon alfa-2a;peginterferon alfa-2b;ribavirin

IFNL3 (also called IL28B in older literature) is linked to how well the immune system responds to interferon-based treatment for hepatitis C. Triple therapy (peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin, sometimes with telaprevir) was used to treat chronic hepatitis C infection. Peginterferon alfa-2a and peginterferon alfa-2b are antiviral immune-stimulating injections, and ribavirin is an antiviral taken by mouth; telaprevir is an older direct-acting antiviral that was used with them for some hepatitis C types.

CYP2D6

*1/*2x2 | Ultrarapid Metabolizer

Affected medications: imipramine, codeine, amitriptyline, tamoxifen

CYP2D6 is an enzyme that activates or clears many medications. As an ultrarapid metabolizer, you may process some drugs so quickly that they are less effective, while other drugs (notably some opioids) can be converted to active forms more quickly, increasing side-effect risk. Codeine is an opioid pain and cough medicine that must be converted to morphine to work; ultrarapid metabolism can increase morphine levels and side effects (excessive sleepiness, slowed breathing).

CYP2B6

*1/*9 | Likely Intermediate Metabolizer

Affected medications: Bupropion, Efavirenz, Methadone, Sertraline

CYP2B6 helps the body break down several antidepressants, HIV/viral medicines, and some opioids. With intermediate metabolism, drug levels may be higher or lower than expected depending on the medication. Bupropion (Wellbutrin) is an antidepressant also used to help with smoking cessation. Efavirenz and nevirapine are antiviral medicines used as part of HIV treatment. Methadone (Dolophine, Methadose) is an opioid used for chronic pain and for opioid use disorder treatment; changes in metabolism can affect both pain control and side effects like sedation or breathing suppression.

What You Carry (Family Planning)

You're a healthy carrier for 3 conditions. These don't affect your health, but they matter if you're planning to have children.

SMN1

Spinal Muscular Atrophy

SMA is usually inherited in an autosomal recessive way. If your reproductive partner is also an SMN1 carrier, each pregnancy would have a 25% (1 in 4) chance to be affected with SMA, a 50% chance for the child to be a carrier, and a 25% chance to inherit two working copies. Because this is a high-priority finding, carrier testing for your partner is strongly recommended (including SMN1 copy

number testing and discussion of residual risk, as some carriers can have two copies on one chromosome). If both partners are carriers, options to consider include IVF with preimplantation genetic testing (PGT-M), prenatal testing during pregnancy (CVS or amniocentesis), use of donor egg/sperm, or adoption. A genetics professional can help review these options in a way that fits your values and timeline.

CPT2

Encephalopathy, Acute, Infection-Induced, Susceptibility To, 4

This condition is typically inherited in an autosomal recessive way. If your reproductive partner is also a carrier for a CPT2-related condition, each pregnancy would have a 25% chance to be affected, a 50% chance for the child to be a carrier, and a 25% chance to inherit two working copies. Because this is marked high priority, partner testing is recommended. If both partners are carriers, options can include IVF with PGT-M, prenatal diagnostic testing (CVS or amniocentesis), or use of donor egg/sperm. A genetic counselor can help confirm the specific variant, discuss test limitations, and coordinate partner testing.

DUOXA2

Inherited Thyroid Metabolism Disease

DUOXA2-related thyroid metabolism conditions are usually autosomal recessive. If your reproductive partner is also a DUOXA2 carrier, each pregnancy would have a 25% chance to be affected, a 50% chance to be a carrier, and a 25% chance to inherit two working copies. Because this is a high-priority carrier finding, partner testing is recommended. If both partners are carriers, you can consider options such as IVF with PGT-M or prenatal diagnostic testing (CVS or amniocentesis). Regardless, newborn screening commonly checks for hypothyroidism, and early treatment is very effective—your healthcare team can help you plan the approach that feels right for you.

Your Heart Health Risk

Lipoprotein(a), or Lp(a), is a genetically determined cholesterol particle linked to heart disease risk. Unlike regular cholesterol, it can't be lowered with diet or statins.

Lp(a)

Moderate Cardiovascular Risk

Your Lipoprotein(a) is in the moderate range based on your genetics. Lp(a) is a cardiovascular risk factor that's largely inherited. Consider getting a direct Lp(a) blood test if you have other risk factors or family history of early heart disease.

HLA Drug Safety

HLA genes shape your immune system. Certain HLA types can cause severe drug reactions, so screening identifies which medications are safe for you.

HLA Screening

No Risk Alleles (41 genes typed)

Your HLA genes were screened for known drug hypersensitivity alleles. No risk variants were detected. Based on your HLA type, you are genetically cleared for: abacavir, allopurinol, antiepileptics, carbamazepine, dapsone, flucloxacillin, lamotrigine, methazolamide, oxcarbazepine, phenytoin, sulfamethoxazole / trimethoprim.

Additional Genetic Variants

Your genome also contains 10 genes where one copy doesn't work normally (loss-of-function variants). For most of these, having one working copy is enough, but they may contribute to subtle differences in how your body works.

GSTA4

Glutathione detoxification of lipid peroxidation (4-HNE clearance)

GSTA4 is an important gene that helps protect our cells by detoxifying harmful substances. When loss-of-function variants occur in this gene, the enzyme it produces becomes less effective at cleaning up toxic byproducts. This means that cells might not be able to manage oxidative stress as well, potentially leading to increased damage over time.

Your variant: You're heterozygous (a 'carrier') for rs749259552 in GSTA4, meaning you have one copy of this variant and one typical copy. For many detox/antioxidant genes, carriers often feel completely normal in day-to-day life because one working copy can be enough.

PCSK4

Sperm capacitation → acrosome reaction → egg binding (PCSK4-dependent protein activation)

PCSK4 is a gene that produces an enzyme important for turning inactive protein precursors into active molecules, a process essential for normal reproductive functions in both men and women. When the gene has loss of function variants, the enzyme may not work properly, which can interfere with fertility by affecting sperm development, egg processing, and overall reproductive health.

Your variant: You're a heterozygous carrier (one copy G, one copy A) of rs200944148 in PCSK4. Based on the papers provided, there isn't evidence that single-copy carriers have a consistent medical syndrome. If PCSK4 variants matter clinically, the most biologically plausible area is fertility—especially sperm function—because PCSK4 is mainly active in sperm and testicular germ cells.

ITIH2

Hyaluronan (HA) matrix stabilization by the inter-alpha-trypsin inhibitor (ITI) family

ITIH2 is a gene that plays an important role in keeping the material between our cells stable and in managing inflammation. When there are changes or variants that reduce the gene's normal activity (known as loss-of-function variants), the protein may not work as well as it should. This reduction can affect processes like wound healing and may be linked with diseases such as certain types of cancer.

Your variant: With one copy of rs151229507 (G/C), you are a heterozygous carrier. Based on the papers reviewed, there is no documented 'ITIH2 carrier condition' and no evidence that carriers routinely develop a predictable set of symptoms.

TLR10

TLR signaling “volume control” (MyD88/TRIF → NF-κB & interferon pathways)

TLR10 is a gene that normally acts as a brake on the immune system, helping to keep inflammation under control. When there are loss-of-function changes—mutations that lower or stop the gene’s normal activity—this braking effect is weakened, which may lead to an overactive immune response and a greater chance of inflammation-related problems.

Your variant: With a **heterozygous (G/T)** result for rs187892716, you have one copy of the variant and one typical copy. For most immune-related SNPs, this usually means any effect—if there is one—is modest and shows up as a *tilt* in how strongly you react to infections or inflammation, not a clear-cut disease.

TMEM59

Microglial inflammasome/pyroptosis control (NLRP3 → Caspase-1 → IL-1β/IL-18) with NF-κB “priming”

TMEM59 is a gene responsible for making a protein that plays key roles in how cells communicate, clean themselves up, and process other proteins. When the gene doesn’t work as it should (a loss of function), it can disturb these processes, which may affect conditions like Alzheimer’s disease and stroke.

Your variant: You carry one copy (C/T) of rs200790405 in TMEM59. Based on the papers provided, there is no direct evidence that heterozygous carriers of this specific variant develop a predictable set of symptoms. What *is* known is that TMEM59 is a ‘dial’ in immune/inflammation and cellular cleanup pathways—especially in microglia.

SMIM22

Cancer-cell “sugar-burning” (glycolysis) growth program linked to SMIM22/GALE

SMIM22 is a gene that provides instructions to make a small protein embedded in the cell membrane. This protein plays important roles in controlling how cells use energy and how quickly they grow. When SMIM22 loses its normal function due to genetic changes or mutations, it can disrupt these processes. For everyday understanding, think of it as a switch that helps regulate cell behavior – if the switch fails, the normal balance of cell activities may be disturbed, which can affect cancer development and progression.

Your variant: Right now, based on the papers you provided, there is no evidence that people who carry rs778473760 in SMIM22—whether heterozygous or homozygous—have a predictable set of symptoms. The literature you shared focuses on SMIM22 as a gene that tumors may turn up or down, and how that relates to tumor behavior.

KLHL35

Ubiquitin “tag-and-recycle” protein quality-control (KLHL adaptors)

KLHL35 is a gene that produces a protein playing a vital role in keeping our cells healthy by helping to tag and recycle proteins. This process is key to making sure cells have just the right mix of proteins to function correctly. When there are loss-of-function changes—variants that reduce or shut down the gene’s normal activity—the gene may not do its job properly, potentially disrupting the cell’s balance.

Your variant: Based on the papers you provided, being heterozygous for rs756778027 in KLHL35 does not come with a known, predictable ‘carrier symptom’ pattern. The research here mostly treats KLHL35 as a gene whose activity level (expression) or epigenetic state (methylation) changes in certain diseases—especially cancers—and as a contributor to statistical risk/prognosis models.

ZNF425

MAPK "stress-to-gene-expression" signaling (AP-1/SRE/SRF output)

ZNF425 normally produces a protein that acts like a regulator, helping to turn off certain genes during early development—especially in the heart. When the gene doesn't work as it should due to loss-of-function variants, its ability to control these critical processes is reduced.

Your variant: Based on the papers you provided, being heterozygous for rs769014744 in ZNF425 does not currently have a documented, predictable set of symptoms. The main evidence is from cell experiments showing what ZNF425 can do when over-expressed or knocked out in lab cell lines, not what naturally occurring carrier variants do in living people (Papers 1–2).

FLG2

Skin barrier cornification & corneodesmosome adhesion (the 'brick-and-mortar' barrier)

FLG2 is a gene that produces filaggrin-2, an important protein for healthy skin. It helps form the skin's protective outer layer, keeps the skin moisturized, and defends against environmental germs. When mutations cause a loss of function in this gene, the resulting protein may be truncated or not produced correctly, which can weaken the skin's natural barrier.

Your variant: Because you're heterozygous (one copy) for rs556285121, the big question is whether a single altered copy meaningfully lowers FLG2 function. In the papers reviewed, clear, severe FLG2 diseases (like peeling skin syndrome) were reported when people had two nonworking copies (homozygous loss-of-function), not in single-copy carriers (PMID: 29758285; PMID: 28884927).

ZNF492

Gene regulation via promoter binding (ZNF492 as a transcription "dimmer switch")

ZNF492 is a gene that provides instructions for making a protein which helps control other genes in our cells. By binding to DNA, this protein plays a role in regulating cellular activities. When changes occur that reduce or eliminate the normal function of this gene—what scientists call loss-of-function variants—it can disrupt the fine-tuning of gene activity and may have implications for health, including links to kidney cancer.

Your variant: Based on the reviewed papers, there is no documented symptom pattern for people who carry rs370410008 in ZNF492—either heterozygous or homozygous.

What This Means For You

Based on your complete genetic picture, here are the most important things to understand. Each insight is backed by research on your specific variants.

1. Avoid prolonged fasting and don't push hard workouts when sick (especially for **CPT2**).

   Why: CPT2 is part of long-chain fat burning; fasting and fever/exertion increase reliance on this pathway. Rare carriers can have CPT2-type muscle symptoms under stacked stress, so steady fueling and skipping hard sessions during illness meaningfully reduces risk.

Based on: CPT2

2 Prioritize partner testing for **SMN1**, **CPT2**, and **DUOXA2** before pregnancy.

Why: You are a confirmed carrier for **SMN1** (SMA), **CPT2** (fat-to-energy metabolism disorder risk in affected children), and **DUOXA2** (thyroid hormone synthesis disorder risk in affected children). Carriers are usually healthy, but if a partner is also a carrier for the same gene, each pregnancy can have a 25% chance of being affected—so partner testing is the highest-impact next step.

Based on: SMN1, CPT2, DUOXA2

3 Have one clear illness plan: rest, hydrate, add carbs early, and escalate care quickly for breathing or mental-status changes (CPT2 + **ITIH2/TLR10/TMEM59**).

Why: During infection, **CPT2** risk is mainly from low intake/catabolism, while **ITIH2**, **TLR10**, and **TMEM59** sit in inflammation/immune-response pathways where severe infections are the relevant stress-test. A unified early-rest/early-care approach prevents you from stacking risks.

Based on: CPT2, ITIH2, TLR10, TMEM59

4 Use symptom-triggered testing: check **TSH/free T4** if persistent low-energy/cold intolerance (DUOXA2) and check **CK/kidneys** urgently for dark urine or severe muscle pain (CPT2).

Why: DUOXA2 carriers are usually well, but some monoallelic carriers show thyroid variability—symptoms are the right trigger for labs. **CPT2** is the key gene where prompt testing during red-flag episodes can prevent kidney complications from rhabdomyolysis.

Based on: DUOXA2, CPT2

5 AVOID imipramine, codeine - you're an ultrarapid metabolizer (CYP2D6) which can cause dangerous drug levels.

Why: Your body converts these medications to their active form much faster than normal, which can lead to overdose effects even at standard doses.

Based on: CYP2D6

6 Treat barrier and oxidative-load prevention as 'multi-gene coverage': no smoking, avoid binge drinking, strong skin care, and dental care (**GSTA4/FLG2/KLHL35**).

Why: GSTA4 supports detox of oxidative lipid byproducts and is highlighted in periodontitis and toxin/oxidant contexts; **FLG2** supports skin barrier integrity and is stress/heat/friction sensitive; **KLHL35** appears in inflammation/cancer-context literature where smoking is a major modifier. These habits reduce shared inflammatory/oxidative strain.

Based on: GSTA4, FLG2, KLHL35

7 You may need lower doses of Tacrolimus, Quetiapine (Seroquel®) due to slow metabolism (CYP3A5).

Why: Your body processes these medications more slowly, so standard doses may build up and cause side effects.

Based on: CYP3A5

8 Consider getting a direct Lp(a) blood test - your genetics suggest moderate cardiovascular risk from this inherited factor.

Why: Lp(a) is a lipid particle that increases heart disease risk independently of LDL cholesterol.

Based on: LPA

Your Biological Pathways & Conditions

Your genetic variants affect these major biological systems. Understanding which pathways, processes, and disease risks are involved helps explain how your body functions.

Energy Metabolism — 1 gene

How your body converts fats, sugars, and other nutrients into usable energy (ATP)

Affected genes: CPT2

PROCESS	Fatty acid degradation	Breaking down fats for energy
PROCESS	Fatty acid metabolism	Processing dietary and stored fats

WHY IT MATTERS:

Hormone Systems — 2 genes

Endocrine pathways that regulate metabolism, growth, and energy balance

Affected genes: CPT2, DUOXA2

PATHWAY	PPAR signaling pathway	Metabolic regulation
PROCESS	Thyroid hormone synthesis	Thyroid function

WHY IT MATTERS:

Your CPT2 variant reduces the ability to burn long-chain fats for energy during fasting, illness, or prolonged exercise - potentially causing muscle breakdown and energy crisis.

CPT2 plays a role in metabolic hormone signaling; your variant may affect how your body regulates energy balance. Your DUOXA2 variant may reduce hydrogen peroxide production needed for thyroid hormone synthesis, potentially affecting metabolism and energy levels.

Cardiovascular

1 gene

Heart and blood vessel function, including disease risk pathways

Affected genes: CPT2

DISEASE	Diabetic cardiomyopathy	Heart disease risk

WHY IT MATTERS:

Fatty acid metabolism affects heart muscle energy supply; your CPT2 variant may increase cardiac stress during metabolic challenges.

Drug Metabolism (CYP450)

1 gene

The liver enzymes that process medications, affecting drug dosing and effectiveness

Affected genes: GSTA4

PROCESS	Metabolism of xenobiotics by cytochrome P450	Toxin processing
PROCESS	Drug metabolism - cytochrome P450	Phase I drug processing

WHY IT MATTERS:

GSTA4 helps process certain drugs and their metabolites; your variant may alter how quickly you clear some medications.

Detoxification

1 gene

Systems that neutralize toxins, free radicals, and waste products

Affected genes: GSTA4

PROCESS	Glutathione metabolism	Antioxidant defense

WHY IT MATTERS:

Your GSTA4 variant reduces glutathione-based detoxification, potentially increasing sensitivity to oxidative stress and certain toxins.

Your Monitoring Plan

Regular monitoring helps you stay ahead of any issues. Here's what to track and why:

Essential Tests

Partner carrier testing: SMN1 copy number; CPT2 and DUOXA2 targeted testing

Determines reproductive risk for confirmed carrier conditions and informs options (PGT-M/prenatal testing).

Before pregnancy or as early as possible in family planning

For: CPT2, DUOXA2, SMN1

Creatine kinase (CK), kidney function (BMP/creatinine), urine myoglobin/urinalysis

Rapidly confirms/excludes rhabdomyolysis and protects kidneys—main actionable CPT2-associated acute scenario.

Same-day whenever dark urine occurs or severe muscle pain/weakness follows exertion or illness

For: CPT2

Recommended Tests

TSH and free T4

Screens for treatable hypothyroidism if DUOXA2 carrier state is clinically expressing in a borderline way.

Symptom-triggered (persistent fatigue/cold intolerance/slow recovery > a few weeks) or per clinician discretion

For: DUOXA2

Age-appropriate cancer screening (standard-of-care)

SMIM22/KLHL35/ZNF492 findings are not diagnostic but support being consistent with routine screening.

Per national guidelines and personal/family history

For: SMIM22, KLHL35, ZNF492

Dental exams/cleanings

Reduces chronic periodontal inflammation/oxidative stress burden highlighted in GSTA4-related literature.

Per standard dental schedule (often every 6 months; individualized)

For: GSTA4

Optional/Situational

25(OH) Vitamin D

Modifiable factor supporting immune function; aligns with TLR10 supportive strategy.

Once baseline; repeat 3–6 months after supplementation if low (or per clinician)

For: TLR10

Dermatology evaluation

Addresses FLG2-linked barrier vulnerability with evidence-based escalation if needed.

As needed if persistent eczema/peeling or recurrent skin infections

For: FLG2

Prioritized Recommendations

Based on analysis of all your genetic variants, here are the most important actions organized by category:

Lifestyle	6
Nutrition & Diet	5
Exercise	3
Supplements	4
Pharmaceuticals	6
Labs to Check	4
Symptoms to Watch	6
Things to Avoid	6

Lifestyle

Partner Testing First: SMN1/CPT2/DUOXA2 HIGH

For reproductive planning, prioritize **partner carrier testing** for **SMN1 (SMA)** first, and also for **CPT2** and **DUOXA2** (confirm variant and testing method). If both partners are carriers for any of these, discuss options such as IVF with PGT-M, prenatal diagnostic testing (CVS/amniocentesis), or donor gametes with a genetics professional.

For: CPT2, DUOXA2, SMN1

Sleep & Recovery as Medicine HIGH

Aim for a consistent sleep schedule and build in recovery after hard days. When you're run down or sick, deliberately lower training intensity/volume and prioritize rest.

For: CPT2, TLR10, TMEM59, SMIM22

Early Care for Serious Infections HIGH

If you develop a significant infection (high fever, rapidly worsening symptoms, or breathing symptoms), don't 'tough it out.' Rest, hydrate, and seek earlier medical advice—especially for shortness of breath, confusion, or inability to keep fluids down.

For: CPT2, ITIH2, TLR10, TMEM59

No Smoking, Minimize Secondhand Smoke HIGH

Treat smoking cessation/avoidance and minimizing secondhand smoke as a top prevention lever. If you currently smoke, consider formal cessation support.

For: GSTA4, KLHL35

Barrier Care Daily (Skin + Teeth) MODERATE

Keep daily skin barrier care (short lukewarm showers, gentle fragrance-free cleanser only where needed, moisturize within 3 minutes, humidifier in dry seasons, minimize friction). Pair that with strong oral hygiene

Nutrition & Diet

Avoid Prolonged Fasting HIGH

Avoid long fasts or aggressive intermittent fasting. Aim to eat within 1–2 hours of waking and then every ~3–4 hours while awake; increase frequency when active or unwell.

For: CPT2

Carb Support Before Endurance MODERATE

Before endurance-style exercise, take in carbohydrates. If you ever develop clear CPT2-type symptoms, discuss whether MCT strategies are appropriate with a clinician familiar with fatty-acid oxidation disorders.

For: CPT2

Adequate Iodine, Avoid Megadoses MODERATE

Use iodized salt at home (unless you must restrict sodium) and include iodine-containing foods you tolerate (dairy/seafood/eggs). Avoid high-dose iodine or 'thyroid support' products unless advised by a clinician.

For: DUOXA2

Anti-Inflammatory, Fiber-Forward Default MODERATE

Use a Mediterranean-leaning, fiber-forward pattern most days (vegetables/legumes, nuts/olive oil, fish; limit ultra-processed foods).

For: TLR10, TMEM59, KLHL35

Alcohol: Avoid Binge Patterns MODERATE

If you drink, avoid binge drinking, don't drink on an empty stomach, and hydrate/eat with alcohol.

For: GSTA4

(clean between teeth most days + regular dental cleanings).

For: FLG2, GSTA4

Fertility: Evaluate Earlier if Trying

MODERATE

If fertility is a current goal and conception is not happening as expected (6–12 months, or sooner depending on age/known factors), consider earlier fertility evaluation and ask whether sperm function testing is appropriate (not only count/motility).

For: PCSK4

Exercise

Moderate, Consistent Training Baseline

HIGH

Favor steady, moderate exercise as your default. If increasing intensity, ramp up gradually over weeks and schedule recovery (easy day after hard day).

For: CPT2, TLR10, TMEM59, KLHL35, SMIM22, GSTA4

Don't Train Hard When Sick

HIGH

Reschedule hard workouts when you have fever, flu-like illness, or you're overheating; return gradually once fully recovered.

For: CPT2, TLR10, TMEM59

Protect Skin During Workouts

HELPFUL

During/after workouts: choose low-friction clothing, shower soon after sweating with a gentle cleanser, and re-moisturize.

For: FLG2

Supplements

Don't Start Carnitine Blindly

MODERATE

Do not start carnitine supplements on your own. If you ever develop recurrent CPT2-type symptoms, discuss supplements and whether free carnitine testing is appropriate with a clinician familiar with FAODs.

For: CPT2

Iodine Only if Clinically Indicated

MODERATE

Avoid high-dose iodine supplements unless a clinician has confirmed low intake/status and recommended a specific dose.

For: DUOXA2

Check Vitamin D Before Supplementing

HELPFUL

Consider checking a 25(OH)D level and supplement only if low, with clinician guidance.

For: TLR10

Avoid Unneeded Iron Supplements

MODERATE

Do not self-supplement iron unless levels have been checked and your clinician recommends it.

For: GSTA4

Pharmaceuticals

CPT2 Options If Symptomatic

MODERATE

If you develop recurrent rhabdomyolysis or clear CPT2-related exercise intolerance, discuss **bezafibrate** and other FAOD management strategies with a metabolic specialist; do not start as an asymptomatic carrier without specialist input.

For: CPT2

Levothyroxine If Hypothyroid

MODERATE

Labs to Check

TSH & Free T4 If Symptoms

MODERATE

If you develop persistent fatigue, brain fog, low mood, constipation, cold intolerance, or slow exercise recovery for more than a few weeks, ask for **TSH and free T4**. Consider exam/ultrasound if neck fullness/goiter develops.

For: DUOXA2

CK/Kidneys for Dark Urine

HIGH

If thyroid labs show hypothyroidism, discuss levothyroxine with your clinician as standard replacement therapy.

For: DUOXA2

Cisplatin: Proactive Ear/Kidney Monitoring

MODERATE

If cisplatin chemotherapy is ever used, proactively request baseline and follow-up hearing and kidney monitoring and report early tinnitus/hearing change promptly.

For: GSTA4

Mention TLR10 Context in RA Therapy

HELPFUL

If you ever develop rheumatoid arthritis and infliximab is considered, you can mention that functional TLR10 variation has been linked to response differences (not rs187892716 specifically) and ask your rheumatologist if it's clinically relevant.

For: TLR10

Dermatology Step-Up for Dermatitis

HELPFUL

If you develop moderate-to-severe atopic dermatitis not controlled with topical therapy, ask a dermatologist whether dupilumab (or other type-2 targeted therapy) is appropriate.

For: FLG2

Avoid Casual Systemic Steroids

HELPFUL

Avoid using systemic steroids casually for minor symptoms; use only for clear medical indications.

For: TMEM59

If you have severe muscle pain/weakness after exertion or illness, or dark/cola-colored urine, seek same-day evaluation for **CK**, **kidney function**, and urine myoglobin/urinalysis.

For: CPT2

Vitamin D Level (If Useful)

HELPFUL

Check **25(OH)D** once as a baseline (or per clinician preference) and recheck after treatment if low.

For: TLR10

Urinalysis/Kidney Labs If Signs

MODERATE

If you develop foamy urine, blood in urine, swelling, or new high blood pressure, ask for **urinalysis** and **kidney function** labs.

For: ITIH2

Symptoms to Watch

CPT2 Muscle/Rhabdo Warning Signs

HIGH

Stop activity and cool down if you get deep muscle burning/cramps/unusual weakness; seek urgent care the same day for dark urine or symptoms that don't improve quickly and mention **CPT2 carrier status**.

For: CPT2

Thyroid Drift Clues

MODERATE

Track persistent fatigue, brain fog, cold intolerance, constipation, hair/skin changes, or neck fullness; request TSH/free T4 if persistent or worsening.

For: DUOXA2

Escalating Infection Red Flags

HIGH

During infections, seek urgent evaluation for shortness of breath, chest pain, confusion, fainting, rapidly worsening symptoms, or inability to keep fluids down.

For: CPT2, ITIH2, TLR10, TMEM59

Things to Avoid

Avoid Fasting + Fever + Hard Exercise

HIGH

Avoid prolonged fasting; avoid hard workouts when febrile/overheating; avoid stacking endurance exercise with extreme heat or cold.

For: CPT2

Tell Anesthesia About CPT2

MODERATE

Before surgery, inform anesthesia you are a **CPT2 carrier**; avoid succinylcholine/halothane exposure without discussion of risks/alternatives.

For: CPT2

Avoid High-Dose Iodine Products

MODERATE

Avoid high-dose iodine supplements or "thyroid support" products unless prescribed.

For: DUOXA2

Avoid Smoking and Binge Drinking

HIGH

Skin Infection/Barrier Breakdown

MODERATE

For rapidly spreading redness/warmth, pus, increasing pain, or fever with skin symptoms, seek urgent care; for persistent itch/peeling, intensify barrier care and consider dermatology.

For: FLG2

Dental Inflammation Signals

MODERATE

Bleeding gums, persistent swelling, or loose teeth should prompt dental evaluation and a tailored home-care plan.

For: GSTA4

Fertility Timing Trigger

MODERATE

If trying to conceive and it's taking longer than expected, consider fertility consultation and mention PCSK4; ask about sperm function testing when appropriate.

For: PCSK4

Avoid smoking and avoid binge drinking; keep alcohol modest if used.

For: GSTA4, KLHL35

Avoid Harsh Soaps/Overheating Skin

MODERATE

Avoid harsh/high-pH soaps and prolonged hot baths/saunas if they trigger flares; reduce friction from tight/rough clothing; avoid sunburn.

For: FLG2

Avoid DIY Hypobaric Protocols

HELPFUL

Avoid self-directed hypobaric/pressure 'anti-aging' protocols outside supervised settings.

For: TMEM59

Lab Markers & Monitoring

These lab values from your records are particularly relevant to your genetic findings. Tracking them over time can help monitor your specific genetic conditions.

Data from 2012-06-12 to 2026-01-08 (410 unique markers)

Albumin/Creatinine Ratio, Random Urine

Attention needed

Latest Value

14.3 mcg/mg crt

Average: 8.66 | 18 readings

Trend Over Time

In animal models, Gsta4 protects against cisplatin ototoxicity and is involved in protective transcriptional responses in cisplatin kidney injury. Monitoring helps catch toxicity early.

Relevant to: GSTA4

⚠ 2 Alert(s): 2024-08-05 (14.3), 2024-02-10

BUN

Attention needed

Latest Value

25 mg/dL

Average: 20.97 | 54 readings

Trend Over Time

In animal models, Gsta4 protects against cisplatin ototoxicity and is involved in protective transcriptional responses in cisplatin kidney injury. Monitoring helps catch toxicity early.

Relevant to: GSTA4

⚠ 1 Alert(s): 2024-10-26 (40)

(35.1)

C-Reactive Protein (CRP)

Attention needed

Latest Value

0.04 mg/L

Average: 0.27 | 2 readings

Trend Over Time

A TLR10 polymorphism (rs11725309 CT) was associated with higher CRP in RA patients, and TLR10 broadly regulates inflammatory signaling; CRP is a simple way to track systemic inflammation if you have symptoms.

Relevant to: TLR10

⚠ 1 Alert(s): 2024-01-29 (0.5)

Creatine Kinase

Attention needed

Latest Value

807.0 U/L

Average: 318.1 | 10 readings

Trend Over Time

CK rises when muscle is injured. Because CPT2-related problems can present as rhabdomyolysis after triggers (exercise, fever), checking CK during symptoms helps confirm whether muscle breakdown is happening.

Relevant to: CPT2

⚠ 1 Alert(s): 2025-11-26 (807.0)

Creatinine

Attention needed

Latest Value

1.06 mg/dL

Average: 1.1 | 53 readings

Trend Over Time

In animal models, Gsta4 protects against cisplatin ototoxicity and is involved in protective transcriptional responses in cisplatin kidney injury. Monitoring helps catch toxicity early.

Relevant to: GSTA4

⚠ 1 Alert(s): 2012-06-12 (1.73)

Creatinine, Random Urine

Attention needed

Latest Value

53.96 mg/dL

Average: 98.96 | 22 readings

Trend Over Time

In animal models, Gsta4 protects against cisplatin ototoxicity and is involved in protective transcriptional responses in cisplatin kidney injury. Monitoring helps catch toxicity early.

Relevant to: GSTA4

⚠ 3 Alert(s): 2024-04-10 (185.0), 2024-04-10 (185.0), 2023-11-04 (158.2)

Ferritin

Attention needed

Latest Value

Iron

Attention needed

Latest Value

38 ng/mL

Average: 80.48 | 39 readings

Trend Over Time

Iron overload drives oxidative stress and induces GSTA4 in mouse liver/kidney; knowing your iron status helps avoid unnecessary oxidative burden from excess iron.

Relevant to: GSTA4

⚠ 7 Alert(s): 2023-10-27 (123.3), 2023-02-27 (130.5), 2023-02-22 (152.4) and 4 more

86 mcg/dL

Average: 87.39 | 38 readings

Trend Over Time

Iron overload drives oxidative stress and induces GSTA4 in mouse liver/kidney; knowing your iron status helps avoid unnecessary oxidative burden from excess iron.

Relevant to: GSTA4

⚠ 6 Alert(s): 2025-09-24 (148.0), 2021-07-26 (133.0), 2018-06-19 (140.0) and 3 more

T4 (Thyroxine), Total

Attention needed

Latest Value

9.1 mcg/dL

Average: 11.95 | 29 readings

Trend Over Time

These are the most direct way to see if your thyroid hormone production is keeping up. DUOXA2/DUOX variants can present with mild/borderline patterns in some cases, so checking both TSH and FT4 gives a clearer picture than TSH alone.

Relevant to: DUOXA2

⚠ 1 Alert(s): 2024-10-27 (113.0)

T4 Free (FT4)

Attention needed

Latest Value

1.6 ng/dL

Average: 2.02 | 45 readings

Trend Over Time

These are the most direct way to see if your thyroid hormone production is keeping up. DUOXA2/DUOX variants can present with mild/borderline patterns in some cases, so checking both TSH and FT4 gives a clearer picture than TSH alone.

Relevant to: DUOXA2

⚠ 2 Alert(s): 2024-01-29 (17.7), 2021-07-26 (17.1)

TSH

Attention needed

Latest Value

2.62 mIU/L

Average: 1.82 | 52 readings

Trend Over Time

Vitamin D, 25-Hydroxy, Total

Attention needed

Latest Value

66 ng/mL

Average: 57.47 | 38 readings

Trend Over Time

These are the most direct way to see if your thyroid hormone production is keeping up. DUOXA2/DUOX variants can present with mild/borderline patterns in some cases, so checking both TSH and FT4 gives a clearer picture than TSH alone.

Relevant to: DUOXA2

⚠ 8 Alert(s): 2025-12-26 (2.95), 2025-03-03 (3.37), 2024-02-10 (2.88) and 5 more

Active vitamin D can upregulate TLR10 expression in a monocyte cell model, suggesting vitamin D status could influence how available the 'TLR10 brake' is in some contexts. This is mechanistic evidence, not proven clinical benefit, but testing is low-risk and commonly used.

Relevant to: TLR10

⚠ 2 Alert(s): 2024-01-29 (90), 2023-11-04 (94.32)

Vitamin D3

Attention needed

Latest Value

57 ng/mL

Average: 57.8 | 30 readings

Trend Over Time

Active vitamin D can upregulate TLR10 expression in a monocyte cell model, suggesting vitamin D status could influence how available the 'TLR10 brake' is in some contexts. This is mechanistic evidence, not proven clinical benefit, but testing is low-risk and commonly used.

Relevant to: TLR10

⚠ 2 Alert(s): 2024-01-29 (90), 2023-11-04 (94.3)

hs-CRP

Attention needed

Latest Value

0.6 mg/L

Average: 0.53 | 34 readings

Trend Over Time

A TLR10 polymorphism (rs11725309 CT) was associated with higher CRP in RA patients, and TLR10 broadly regulates inflammatory signaling; CRP is a simple way to track systemic inflammation if you have symptoms.

Relevant to: TLR10

⚠ 6 Alert(s): 2025-12-26 (0.9), 2025-09-24 (1.1), 2024-10-15 (0.91) and 3 more

BUN/Creatinine Ratio

Trending up

Latest Value

24 x100%

Average: 19.38 | 31 readings

Trend Over Time

Carnitine, Total

Stable

Latest Value

45.1 umol/L

Average: 45.1 | 1 readings

Trend Over Time

In animal models, Gsta4 protects against cisplatin ototoxicity and is involved in protective transcriptional responses in cisplatin kidney injury. Monitoring helps catch toxicity early.

Relevant to: GSTA4

Long-chain acylcarnitines can rise with fasting and exercise in CPT2 deficiency and may reflect metabolic stress. If measured, results depend heavily on whether you were fasting or recently ate/exercised, so standardized timing matters.

Relevant to: CPT2

Creatine Kinase MB (CK-MB)

Trending up

Latest Value

28 U/L

Average: 20.6 | 2 readings

Trend Over Time

CK rises when muscle is injured. Because CPT2-related problems can present as rhabdomyolysis after triggers (exercise, fever), checking CK during symptoms helps confirm whether muscle breakdown is happening.

Relevant to: CPT2

Free T4 Index (T7)

Stable

Latest Value

3

Average: 3 | 1 readings

Trend Over Time

These are the most direct way to see if your thyroid hormone production is keeping up. DUOXA2/DUOX variants can present with mild/borderline patterns in some cases, so checking both TSH and FT4 gives a clearer picture than TSH alone.

Relevant to: DUOXA2

Glucose, Fasting

Stable

Latest Value

65 mg/dL

Average: 97.91 | 45 readings

Trend Over Time

TMEM59-related research is strongest in stroke models, where vascular risk factors drive overall stroke risk more than any single gene. While these tests are not TMEM59-specific, they are practical levers to reduce the main trigger context (ischemic events) studied in the TMEM59 stroke papers. Not documented in reviewed literature as TMEM59-specific monitoring.

Relevant to: TMEM59

Glucose, Random

Stable

Latest Value

108.0 mg/dL

Average: 108.0 | 1 readings

Trend Over Time

TMEM59-related research is strongest in stroke models, where vascular risk factors drive overall stroke risk more than any single gene. While these tests are not TMEM59-specific, they are practical levers to reduce the main trigger context (ischemic events) studied in the TMEM59 stroke papers. Not documented in reviewed literature as TMEM59-specific monitoring.

Relevant to: TMEM59

Transferrin

Stable

Latest Value

279.0 mg/dL

Average: 238.1 | 3 readings

Trend Over Time

Iron overload drives oxidative stress and induces GSTA4 in mouse liver/kidney; knowing your iron status helps avoid unnecessary oxidative burden from excess iron.

Relevant to: GSTA4

Vitamin D, 1,25-Dihydroxy

Stable

Latest Value

37 pg/mL

Average: 37 | 1 readings

Trend Over Time

Active vitamin D can upregulate TLR10 expression in a monocyte cell model, suggesting vitamin D status could influence how available the 'TLR10 brake' is in some contexts. This is mechanistic evidence, not proven clinical benefit, but testing is low-risk and commonly used.

Relevant to: TLR10

Vitamin D2

Trending up

Latest Value

0.96 ng/mL

Average: 0.7 | 10 readings

Trend Over Time

Active vitamin D can upregulate TLR10 expression in a monocyte cell model, suggesting vitamin D status could influence how available the 'TLR10 brake' is in some contexts. This is mechanistic evidence, not proven clinical benefit, but testing is low-risk and commonly used.

Relevant to: TLR10

Vitamin D2, 1,25 (OH)2

Stable

Latest Value

8 pg/mL

Average: 8 | 1 readings

Trend Over Time

Active vitamin D can upregulate TLR10 expression in a monocyte cell model, suggesting vitamin D status could influence how available the 'TLR10 brake' is in some contexts. This is mechanistic evidence, not proven clinical benefit, but testing is low-risk and commonly used.

Relevant to: TLR10

Vitamin D3, 1,25 (OH)2

Stable

Latest Value

37 pg/mL

Average: 37 | 1 readings

Trend Over Time

Active vitamin D can upregulate TLR10 expression in a monocyte cell model, suggesting vitamin D status could influence how available the 'TLR10 brake' is in some contexts. This is mechanistic evidence, not proven clinical benefit, but testing is low-risk and commonly used.

Relevant to: TLR10

Polygenic Risk Profile

Based on analysis of **1036** genetic markers, your polygenic risk profile shows **13 elevated risk** traits and **142 moderate concern** traits. These scores reflect population-level risk tendencies based on common genetic variants.

Red (13) Orange (142) Yellow (603) Green (256)

Highest Priority PRS Findings

Prostate Cancer
More likely to get prostate cancer
CANCER

ApoB
Predisposed to higher ApoB levels
CARDIOVASCULAR

Melanoma
More likely to get melanoma
CANCER

ADH1B (Alcohol Sensitivity)
Predisposed to higher ADHB1 activity
NUTRITION

Homocysteine
Predisposed to higher homocysteine levels
OTHER

Nephritis
More likely to have nephritis
OTHER

Fibromyalgia
More likely to have fibromyalgia
OTHER

Vitamin K
Likely increased vitamin K need
NUTRITION

AVPR1A (Blood Pressure / Anxiety / Depression)
Predisposed to a higher AVPR1A activity
CARDIOVASCULAR

Low Neutrophils
More likely to have neutropenia
IMMUNE

Plus 40 additional elevated-risk traits

Risk by Category

Cardiovascular 12 elevated / 73 total	**Digestive** 10 elevated / 34 total	**Nutrition** 9 elevated / 37 total
Neurological 9 elevated / 39 total	**Immune** 8 elevated / 52 total	**Musculoskeletal** 7 elevated / 37 total
Hematological 5 elevated / 24 total	**Metabolic** 5 elevated / 37 total	

✓ **HLA Screening Complete** - No drug sensitivity alleles detected (41 HLA genes typed)

Lipoprotein(a) Cardiovascular Risk

29.5

KIV2 Copies

MODERATE RISK

Estimated Lp(a): moderate

Your KIV2 copy number (29.5) is in a range associated with a **moderately elevated Lp(a)** level and therefore **moderate added cardiovascular risk**. Lp(a) is a cholesterol-carrying particle that is mostly determined by genetics. Importantly, **fewer KIV2 copies generally mean higher Lp(a)**; in your case, the copy number suggests you're not in the highest-risk group, but you likely have more Lp(a) than average. Higher Lp(a) can contribute to plaque buildup in the arteries (heart attack/stroke risk) and is also linked to aortic valve narrowing in some people. Unlike LDL cholesterol, lifestyle changes usually do **not** lower Lp(a) very much. The practical way to reduce risk is to treat the things we can change—especially **lowering LDL/ApoB**, controlling blood pressure and blood sugar, and avoiding smoking. A blood test provides the clearest picture of your personal Lp(a) level and helps guide how aggressively to manage your other risk factors.

Recommendations

- Confirm with a blood test: Ask your clinician to measure Lp(a) (reported in nmol/L or mg/dL). Lp(a) is largely genetic and usually only needs to be checked once, but a measured value is more accurate than an estimate from genetics.
- Focus on lowering "regular" LDL cholesterol: Because Lp(a) adds extra, lifelong risk, aim for a lower LDL/ApoB target than average—especially if you have other risk factors or a family history of early heart disease. Discuss diet, exercise, and medications (often a statin; sometimes ezetimibe or a PCSK9 inhibitor) with your clinician.
- Review overall risk: Check blood pressure, diabetes/A1c, smoking/vaping, weight, and consider coronary artery calcium (CAC) scoring if your overall risk is uncertain.
- Family implications: Consider Lp(a) testing for first-degree relatives (parents, siblings, children), since Lp(a) runs in families.
- If you have early heart disease, aortic valve stenosis, or very strong family history: Ask about more aggressive LDL lowering and whether you might be a candidate for Lp(a)-lowering therapies as they become available or for clinical trials.

▼ Understanding Lp(a) and KIV2

What is Lp(a)? Lipoprotein(a) is a genetically-determined cholesterol particle that increases cardiovascular risk independent of LDL cholesterol.

KIV2 and Lp(a): The KIV2 copy number has an INVERSE relationship with Lp(a) concentration - fewer copies = smaller Lp(a) particles = HIGHER concentration in blood = HIGHER risk.

Why it matters: Unlike LDL cholesterol, Lp(a) is not significantly affected by diet, exercise, or statins. Knowing your genetic risk helps guide cardiovascular prevention strategies.

Environmental & Lifestyle Factors

Based on your genetic profile, your body may respond differently to certain situations. Understanding these factors helps you make informed lifestyle choices.

Metabolic Stress: Illness

Relevant to: CPT2, ITIH2, TMEM59, KLHL35

What to know: This is your most important shared trigger because it stacks (1) increased energy demand and reduced intake risk (CPT2) with (2) heightened inflammatory/systemic stress biology signals (ITIH2, TMEM59, TLR10) and (3) a general push toward earlier medical evaluation rather than 'waiting it out.' For carriers, this is mainly a preparedness issue—not an expectation of crisis—but it's worth taking seriously.

Practical tip: Use a single sick-day routine: rest early; hydrate; if you can tolerate it, take frequent carbohydrate-containing fluids/foods to avoid a fasting state (CPT2); avoid hard exercise while febrile

(CPT2/TLR10); and seek earlier clinical advice for breathing symptoms, persistent high fever, confusion, or inability to keep fluids down (ITIH2/TMEM59/TLR10).

Psychological: Stress

Relevant to: GSTA4, TLR10, TMEM59, FLG2

What to know: Stress can amplify inflammatory signaling (TLR10, TMEM59), increase oxidative stress load (GSTA4), and worsen barrier function/eczema flares (FLG2). The combined effect is usually gradual (more flares, slower recovery) rather than sudden emergencies.

Practical tip: Treat stress reduction as part of health maintenance: protect sleep consistency (TLR10/TMEM59/CPT2), use a simple daily downshift routine (FLG2), keep exercise moderate/consistent instead of extreme (TLR10/TMEM59/CPT2), and avoid using alcohol as a stress tool (GSTA4).

Environmental: Heat

Relevant to: GSTA4, FLG2

What to know: Heat primarily matters for **skin barrier stress (FLG2)** and **oxidative stress load (GSTA4)**. As heterozygous carriers without a defined syndrome, this is an 'avoid needless stress on the system' situation rather than an emergency risk.

Practical tip: On hot days: choose breathable fabrics, reduce friction, shower soon after sweating and re-moisturize (FLG2), and avoid compounding oxidative stressors like smoking and heavy alcohol (GSTA4).

▼ Symptoms to Be Aware Of

These symptoms may warrant attention in the context of your genetic profile:

- Persistent vomiting or inability to keep fluids down
- Fainting or new confusion
- Sudden severe headache or one-sided weakness
- Chest pain/pressure
- Dark/cola urine
- Severe shortness of breath or chest pain

Supplement-Gene Interactions

Based on analysis of your **180** supplements against your genetic variants: **83 require attention**, **97 appear safe**.

High Risk (33) Moderate (50) Safe (97)

High Caution Required

spermidine

Pathway_overlap

Gene: CPT2

spermidine affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Spermidine is a naturally occurring polyamine that promotes cellular homeostasis and stress resistance largely by inducing autophagy/mitophagy and supporting mitochondrial quality control. Mechanistically it contributes to eIF5A hypusination (via providing aminobutyl groups for hypusine synthesis), enabling translation of specific proteins such as TFEB, a master regulator of lysosomal biogenesis and autophagy; it also modulates inflammatory signaling (e.g., NF-κB/NLRP3) and can influence chromatin/translation through polyamine–nucleic acid interactions.

Recommendation: specialist

lycopene

Pathway_overlap

Gene: CPT2

lycopene affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Lycopene is a non–provitamin A carotenoid that accumulates in lipid membranes and lipoproteins, where it quenches singlet oxygen and scavenges radicals, reduces lipid peroxidation, and modulates redox-sensitive transcription (e.g., NF-κB inhibition, Nrf2 activation) and metabolic regulators (e.g., adiponectin/AMPK, PPARs), leading to anti-inflammatory, cardiometabolic, and potential chemopreventive effects.

Recommendation: specialist

ecklonia-cava-extract-80:1

Pathway_overlap

Gene: CPT2

ecklonia-cava-extract-80:1 affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Ecklonia cava extract (80:1) is a concentrated brown seaweed polyphenol (phlorotannin) preparation that primarily acts as an antioxidant and anti-inflammatory agent, modulating redox-sensitive transcription factors and inflammatory signaling while also influencing carbohydrate and lipid metabolism via enzyme inhibition (e.g., α-glucosidase/α-amylase) and improved insulin signaling in preclinical studies.

Recommendation: specialist

pantethine

Pathway_overlap

Gene: CPT2

pantethine affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Pantethine is the disulfide dimer of pantetheine and a provitamin form of vitamin B5 that is converted to pantetheine/cysteamine and ultimately coenzyme A (CoA). Through raising/redistributing cellular CoA and generating low–molecular-weight thiols, it can modulate lipid synthesis (cholesterol and triglycerides), membrane raft composition, redox status, and phosphatidylserine externalization/microparticle (extracellular vesicle) biogenesis, with downstream anti-inflammatory and vascular-barrier effects in preclinical models.

Recommendation: specialist

reishi-extract-8:1

Pathway_overlap

Gene: CPT2

reishi-extract-8:1 affects multiple pathways related to CPT2. Consult specialist.

astaxanthin

Pathway_overlap

Gene: CPT2

astaxanthin affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Reishi (Ganoderma lucidum) extract (8:1) provides concentrated triterpenoids (ganoderic acids), polysaccharides (β-glucans), and sterols that can modulate innate/adaptive immune signaling (e.g., macrophage/NK cell activity), reduce inflammatory mediator production, and exert antioxidant/mitochondria-protective effects; some constituents may modestly affect glucose and lipid metabolism and platelet function.

Recommendation: specialist

Mechanism: Astaxanthin is a lipid-soluble xanthophyll carotenoid that embeds across cell membranes where it quenches singlet oxygen and scavenges lipid radicals, reducing lipid peroxidation. It also acts as an indirect antioxidant/anti-inflammatory signal modulator (notably activating Nrf2 and downregulating NF-κB), which can improve mitochondrial function, reduce inflammatory cytokine signaling, and limit apoptosis/ferroptosis in stress-exposed tissues (e.g., liver, vasculature, brain).

Recommendation: specialist

melatonin

Pathway_overlap

Gene: CPT2

melatonin affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous indoleamine that primarily signals “biological night” by activating MT1/MT2 GPCRs in the suprachiasmatic nucleus and peripheral tissues, shifting/entraining circadian rhythms and promoting sleep onset. It also acts as a pleiotropic redox modulator: directly scavenges reactive oxygen/nitrogen species, influences mitochondrial function, upregulates antioxidant defenses (e.g., via SIRT1→Nrf2), and modulates immune/inflammatory signaling; in some cancer contexts it can increase ROS within tumor cells to promote apoptosis while protecting normal tissues.

Recommendation: specialist

butyrate

Pathway_overlap

Gene: CPT2

butyrate affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Butyrate (often as sodium/calcium/magnesium butyrate or tributyrin) is a short-chain fatty acid produced by microbial fermentation of fiber that fuels colonocytes, strengthens intestinal barrier function, and modulates immunity and metabolism via GPCR signaling (FFAR2/GPR43, FFAR3/GPR41, HCAR2/GPR109A) and histone deacetylase (HDAC) inhibition, shifting gene expression toward anti-inflammatory, barrier-protective programs.

Recommendation: specialist

maitake

Pathway_overlap

Gene: CPT2

maitake affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Maitake (Grifola frondosa) contains beta-glucans/proteo-beta-glucans and other polysaccharides plus lipid-soluble constituents that act as immunomodulators (pattern-recognition receptor activation), metabolic regulators (PPARδ agonism), and cytoprotective/antioxidant agents, collectively reducing inflammatory signaling, supporting innate/adaptive immune responses, and improving glucose/lipid handling.

Recommendation: specialist

omega-3

Pathway_overlap

Gene: CPT2

omega-3 affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Omega-3 fatty acids (primarily EPA and DHA; ALA as a precursor) incorporate into cell membrane phospholipids and shift lipid mediator production away from arachidonic-acid–derived eicosanoids toward less inflammatory eicosanoids and specialized pro-resolving mediators (resolvins/protectins/maresins). They also modulate gene transcription (e.g., PPARα activation and reduced SREBP-1c signaling), cell signaling and membrane microdomains, improving triglyceride metabolism, inflammation resolution, endothelial function, and potentially muscle protein anabolism in older adults.

Recommendation: specialist

tudca

Pathway_overlap

Gene: CPT2

tudca affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Tauroursodeoxycholic acid (TUDCA) is a hydrophilic taurine-conjugated bile acid that functions as a chemical chaperone and bile-acid signaling molecule. It stabilizes protein folding and membrane integrity, reduces ER stress/unfolded protein response (UPR)–driven apoptosis, modulates bile-acid receptors (e.g., TGR5, FXR; context-dependent), and can improve mitochondrial function and cellular survival signaling in metabolically stressed tissues (liver, pancreas, nervous system).

Recommendation: specialist

c15

Pathway_overlap

Gene: CPT2

c15 affects multiple pathways related to CPT2. Consult specialist.

Mechanism: “C15” in supplement contexts most commonly refers to pentadecanoic acid (C15:0), an odd-chain saturated fatty acid. It can be incorporated into membrane lipids and, when oxidized, yields propionyl-CoA that anaplerotically replenishes succinyl-CoA to support TCA cycle flux; preclinical data also suggest AMPK activation and anti-inflammatory effects that may improve insulin sensitivity and steatotic liver phenotypes.

Recommendation: specialist

coq10

Pathway_overlap

Gene: CPT2

coq10 affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Coenzyme Q10 (ubiquinone/ubiquinol) is an endogenously synthesized lipid-soluble redox carrier in the inner mitochondrial membrane that shuttles electrons from complexes I/II to complex III to support ATP production. In its reduced form (ubiquinol) it also acts as a chain-breaking antioxidant in membranes and lipoproteins and—via the FSP1-CoQ10 system—suppresses lipid peroxidation and ferroptosis.

Recommendation: specialist

cordyceps

Pathway_overlap

Gene: CPT2

cordyceps affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Cordyceps (typically Cordyceps militaris extracts, Ophiocordyceps sinensis mycelia, or fermented “Bailing” products) contains bioactives such as cordycepin (3′-deoxyadenosine), polysaccharides (β-glucan–like heteropolysaccharides), sterols and peptides that modulate immune/inflammatory signaling and cellular energy sensing. Preclinical work suggests polysaccharides reduce inflammatory cytokines and inflammasome activity (e.g., caspase-1/IL-18) and improve barrier/gut-derived endotoxin signaling, while cordycepin activates AMPK and downregulates pro-growth kinases (PI3K/Akt/mTOR, MAPK), thereby improving metabolic inflammation and promoting apoptosis/autophagy in stressed tissues.

Recommendation: specialist

l.-gasseri-bnr17

Pathway_overlap

Gene: CPT2

l.-gasseri-bnr17 affects multiple pathways related to CPT2. Consult specialist.

empagliflozin

Pathway_overlap

Gene: CPT2

empagliflozin affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Lactobacillus gasseri BNR17 is a human milk–derived probiotic strain investigated for anti-obesity and metabolic effects. Preclinical work suggests it modulates host gene expression toward greater fatty-acid oxidation and improved adipose metabolism, likely via microbiome-mediated changes in gut barrier function, bile acid signaling, short-chain fatty acids, and systemic inflammation.

Recommendation: specialist

Mechanism: Empagliflozin is an SGLT2 inhibitor that lowers blood glucose by blocking renal proximal-tubule glucose/sodium reabsorption, causing glucosuria with mild natriuresis/osmotic diuresis. Beyond glycemia, evidence in heart/kidney indicates pleiotropic effects including improved cardiorenal hemodynamics, reduced inflammation/oxidative stress, modulation of myocardial ion handling (putative NHE1 inhibition), improved mitochondrial homeostasis (AMPK-linked mitophagy/fusion), and signaling changes (e.g., Erbb4) that collectively reduce heart failure events and slow CKD progression.

Recommendation: specialist

trigonelline

Pathway_overlap

Gene: CPT2

trigonelline affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Trigonelline is a plant-derived pyridine alkaloid (a niacin/NAD-related metabolite) found in coffee and fenugreek. In preclinical models it improves glucose and lipid homeostasis (e.g., via AMPK and PPARγ signaling), reduces inflammatory and fibrotic signaling (e.g., NLRP3 inflammasome; SPHK1/S1P and Hippo/YAP-TAZ axis), and can modulate cellular redox responses (context-dependent Nrf2 modulation—often inhibitory in cancer models).

Recommendation: specialist

ss31

Pathway_overlap

Gene: CPT2

ss31 affects multiple pathways related to CPT2. Consult specialist.

Mechanism: SS-31 (elamipretide; MTP-131; Bendavia) is a mitochondria-targeted, cell-permeable tetrapeptide that concentrates at the inner mitochondrial membrane by binding cardiolipin. By stabilizing cardiolipin–protein interactions and mitochondrial cristae/supercomplex organization, it reduces cardiolipin peroxidation and cytochrome-c peroxidase activity, lowers mitochondrial ROS generation and proton leak, and improves electron transport efficiency and ATP production.

Recommendation: specialist

arginine

Pathway_overlap

Gene: CPT2

arginine affects multiple pathways related to CPT2. Consult specialist.

Mechanism: L-arginine is a semi-essential amino acid that serves as the primary substrate for nitric oxide synthases (eNOS/nNOS/iNOS) to generate nitric oxide (NO), a key regulator of vascular tone, platelet function, mitochondrial respiration, and glucose/lipid metabolism; it is also a urea-cycle intermediate and a precursor for creatine, polyamines, agmatine, and proline, influencing cell growth, neurotransmission, and wound repair.

Recommendation: specialist

l.-reuteri-dsm

Pathway_overlap

Gene: CPT2

l.-reuteri-dsm affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Limosilactobacillus (Lactobacillus) reuteri DSM 17938 is a probiotic strain that modulates gut microbial ecology and host immune/metabolic signaling. Reported mechanisms include production of microbially derived metabolites (notably short-chain fatty acids such as propionate, and glycerol-derived antimicrobial metabolites like reuterin/3-HPA), enhancement of gut barrier function, and downregulation of pro-inflammatory signaling; preclinical work shows AMPK activation (via propionate) with improved hepatic fatty-acid β-oxidation and reduced oxidative stress/inflammation during toxic or inflammatory insults.

Recommendation: specialist

leucine

Pathway_overlap

Gene: CPT2

leucine affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Leucine is an essential branched-chain amino acid (BCAA) that serves as both a substrate for protein synthesis and a nutrient signal that stimulates muscle anabolism, largely by activating mTORC1. Intracellular leucine is sensed by Sestrin2, which modulates the Rag GTPase–lysosomal amino-acid sensing machinery to increase mTORC1 activity, promoting translation initiation and inhibiting autophagy; leucine is also metabolized to ketoisocaproate (KIC) and the signaling metabolite HMB, which can further reduce proteolysis and support muscle recovery.

Recommendation: specialist

hmb

Pathway_overlap

Gene: CPT2

hmb affects multiple pathways related to CPT2. Consult specialist.

Mechanism: β-hydroxy-β-methylbutyrate (HMB) is a leucine metabolite that supports net muscle protein accretion by increasing muscle protein synthesis (primarily via mTORC1 signaling) and reducing proteolysis (notably via ubiquitin–proteasome and related catabolic pathways), with additional roles in cell-membrane/sarcolemma integrity and recovery from muscle damage. It may also modulate anabolic hormones (GH/IGF-1 axis) and reduce apoptosis/inflammation in some contexts, which can be relevant during disuse, aging, or catabolic stress.

Recommendation: specialist

l-gasseri

Pathway_overlap

Gene: CPT2

l-gasseri affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Lactobacillus gasseri (L. gasseri) is a lactic-acid–producing probiotic whose strain-specific effects include reinforcing mucosal barrier function, producing antimicrobial metabolites (lactate, hydrogen peroxide, bacteriocin-/biosurfactant-like compounds, exopolysaccharides and extracellular vesicles), competing with pathogens for adhesion, and modulating host immunity and metabolism (e.g., dendritic-cell PPARγ signaling, PI3K/Akt anti-inflammatory signaling, and intestinal lipid/fatty-acid sensing impacting glucose homeostasis).

Recommendation: specialist

l-carnitine

Pathway_overlap

Gene: CPT2

l-carnitine affects multiple pathways related to CPT2. Consult specialist.

Mechanism: L-carnitine is an endogenous quaternary amine that shuttles long-chain fatty acids into mitochondria (via CPT1/CACT/CPT2) for β-oxidation and buffers excess acyl-CoA by forming acylcarnitines, supporting cardiac and skeletal muscle energy metabolism. Carnitine and its esters (acetyl-L-carnitine, propionyl-L-carnitine) may also reduce oxidative stress/inflammation and modulate neurotransmission and membrane energetics; however, oral L-carnitine can be converted by gut microbes to trimethylamine (TMA) and then hepatic TMAO, a pathway linked (associatively) to cardiometabolic risk.

Recommendation: specialist

allulose

Pathway_overlap

Gene: CPT2

allulose affects multiple pathways related to CPT2. Consult specialist.

riboflavin

Pathway_overlap

Gene: CPT2

riboflavin affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Allulose (D-psicose) is a rare sugar that tastes sweet but is minimally metabolized in humans; it is absorbed via intestinal hexose transporters and largely excreted unchanged, lowering effective caloric load. It can blunt postprandial glycemia (partly via reduced intestinal carbohydrate digestion/absorption and incretin signaling), modulate appetite-related hypothalamic circuits in animals, and in preclinical models improves adipose and hepatic metabolism via AMPK-SIRT1-PGC-1α and ER-stress/UPR signaling while reducing inflammation and altering gut microbiota/bile acids.

Recommendation: specialist

Mechanism: Riboflavin (vitamin B2) is converted to the flavocoenzymes FMN and FAD, which serve as essential redox cofactors for numerous flavoproteins involved in mitochondrial energy production (electron transfer and acyl-CoA dehydrogenases), antioxidant defense (e.g., glutathione reductase), and cellular signaling; adequate riboflavin supports flavoproteome function, while deficiency impairs bioenergetics and redox homeostasis. In disease models, riboflavin can improve mitochondrial function and activate antioxidant signaling (e.g., SCAD→DJ-1/Keap1→Nrf2) and is also used topically with UVA to generate reactive species that cross-link corneal collagen (keratoconus).

Recommendation: specialist

nmn

Pathway_overlap

Gene: CPT2

nmn affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Nicotinamide mononucleotide (NMN) is a direct NAD+ precursor in the NAD+ salvage pathway (converted to NAD+ via NMNAT enzymes, and may also be dephosphorylated extracellularly to nicotinamide riboside before uptake). By raising cellular NAD+, NMN supports redox reactions and activates NAD+-dependent enzymes (e.g., sirtuins, PARPs) that regulate mitochondrial function, DNA repair, inflammation, and stress responses; multiple animal/cell studies show anti-inflammatory effects including suppression of NLRP3 inflammasome activity/pyroptosis and improved metabolic resilience.

Recommendation: specialist

pqq

Pathway_overlap

Gene: CPT2

pqq affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Pyrroloquinoline quinone (PQQ) is a redox-active quinone best known as a bacterial dehydrogenase cofactor; in mammals it appears to act primarily as a redox modulator and signaling molecule that improves mitochondrial function/biogenesis and reduces oxidative stress and inflammation (e.g., via Nrf2 activation and NF-κB suppression, with upstream involvement of AMPK/PGC-1α and related pathways).

Recommendation: specialist

lysine

Pathway_overlap

Gene: CPT2

lysine affects multiple pathways related to CPT2. Consult specialist.

Mechanism: L-lysine is an essential, cationic amino acid used for protein synthesis and as a precursor for carnitine (via trimethyllysine), supporting fatty-acid transport into mitochondria. Supplemental lysine may also exert osmotic/charge-based effects in the kidney and antimicrobial membrane-disrupting effects at high local concentrations; many cited papers relate to lysine residues as targets of post-translational modifications

agmatine

Pathway_overlap

Gene: CPT2

agmatine affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Agmatine (decarboxylated arginine) acts as an endogenous neuromodulator and polyamine-related metabolite. It modulates imidazoline (I1/I2) and α2-adrenergic receptors, inhibits NMDA receptor signaling (notably GluN2B-dependent) and nitric-oxide synthase–linked pathways, and influences monoaminergic transmission and neurotrophic signaling (e.g., BDNF/CREB/ERK). Peripherally, it can stimulate hepatic mitochondrial fatty-acid oxidation and ureagenesis;

(methylation, neddylation, succinylation, lactylation) rather than effects of lysine supplementation.

Recommendation: specialist

microbiome-derived agmatine has also been reported to activate FXR in mice, affecting GLP-1 and insulin sensitivity.

Recommendation: specialist

serine

Pathway_overlap

Gene: CPT2

serine affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Serine (primarily L-serine) is a conditionally essential amino acid used for protein synthesis and as a central carbon donor into one-carbon/folate metabolism via serine hydroxymethyltransferase (SHMT), generating glycine and 5,10-methylene-THF to support nucleotide synthesis, methylation capacity, and redox balance (via NADPH/glutathione). It also serves as a precursor for phosphatidylserine and sphingolipids and can modulate immune and cancer cell metabolism through effects on anabolic flux, mitochondrial one-carbon reactions, and oxidative stress handling.

Recommendation: specialist

urolithin-a

Pathway_overlap

Gene: CPT2

urolithin-a affects multiple pathways related to CPT2. Consult specialist.

Mechanism: Urolithin A (UA) is a gut microbiota–derived metabolite of ellagic acid/ellagitannins that promotes cellular quality control—especially mitochondrial quality—by inducing mitophagy and improving lysosomal function; it also reduces inflammatory signaling and oxidative stress, partly through Nrf2 activation and suppression of mtDNA-driven innate immune pathways.

Recommendation: specialist

mots-c

Pathway_overlap

Gene: CPT2

mots-c affects multiple pathways related to CPT2. Consult specialist.

Mechanism: MOTS-c is a mitochondria-derived 16–amino acid peptide (a “mitokine”) encoded by mtDNA (12S rRNA) that is induced by metabolic stress/exercise. It can enter the nucleus and reprogram gene expression; intracellularly it perturbs the folate/one-carbon network leading to AICAR accumulation and AMPK activation, improving insulin sensitivity, substrate utilization, mitochondrial stress responses, and anti-inflammatory/antioxidant defenses.

Recommendation: specialist

Moderate Caution

kombucha

Pathway_overlap

Gene: CPT2

mushroom-mix

Pathway_overlap

Gene: CPT2

kombucha affects a pathway related to CPT2. Monitor for effects.

Mechanism: Kombucha is a sweetened tea fermented by a symbiotic culture of bacteria and yeast (SCOBY). Proposed effects arise from (1) microbial exposure (live/viable and dead microbes plus microbial metabolites) that can modulate gut microbiota and intestinal barrier/immune signaling; (2) fermentation-derived organic acids (acetic, gluconic, glucuronic in some products), ethanol and CO2, and transformed tea polyphenols that may influence oxidative stress and metabolic signaling; and (3) tea constituents (polyphenols, caffeine) retained in the final beverage.

Recommendation: monitor

mushroom-mix

Pathway_overlap

Gene: CPT2

mushroom-mix affects a pathway related to CPT2. Monitor for effects.

Mechanism: "Mushroom-mix" is a non-specific blend of medicinal/edible mushroom extracts or powders (commonly reishi, lion's mane, cordyceps, chaga, turkey tail, shiitake/maitake). Across species, key bioactives (β-glucans and other polysaccharides, triterpenes, sterols, phenolics, and in some products cordycepin/ergothioneine) tend to modulate innate/adaptive immunity (e.g., macrophage/NK activity), influence inflammatory signaling, and provide antioxidant/cytoprotective effects; some species also affect neurotrophic signaling (lion's mane) and exercise/oxygen-utilization endpoints (cordyceps).

Recommendation: monitor

chaga

Pathway_overlap

Gene: CPT2

chaga affects a pathway related to CPT2. Monitor for effects.

Mechanism: Chaga (Inonotus obliquus) contains polysaccharides (e.g., β-glucans), phenolics (e.g., DBL/3,4-dihydroxybenzalacetone), melanins, and lanostane-type triterpenoids that appear to modulate immune and inflammatory signaling, redox balance, and cellular energy metabolism. Preclinical studies show anti-proliferative effects via inhibition of NF-κB/STAT3 and induction of AMPK-linked metabolic stress leading to cell-cycle arrest, apoptosis, and/or autophagy; animal models suggest improvements in glucolipid metabolism and renal/endothelial signaling.

Recommendation: monitor

chromium-picolinate

Pathway_overlap

Gene: CPT2

chromium-picolinate affects a pathway related to CPT2. Monitor for effects.

Mechanism: Chromium picolinate provides trivalent chromium with relatively good oral bioavailability; chromium appears to potentiate insulin signaling (likely via chromium-binding peptide chromodulin/LMWCr) by enhancing insulin receptor tyrosine kinase activity and downstream signaling, improving glucose uptake and insulin sensitivity. Additional effects reported in models include AMPK activation, reduced inflammatory signaling (NF-κB), and increased antioxidant response (Nrf2/HO-1); some early concerns suggest picolinate may influence CNS monoamine metabolism, warranting caution in susceptible individuals.

Recommendation: monitor

manganese

Pathway_overlap

Gene: CPT2

manganese affects a pathway related to CPT2. Monitor for effects.

Mechanism: Manganese is an essential trace mineral that functions primarily as an enzyme cofactor (metalloenzyme activator) in antioxidant defense (MnSOD), neurotransmitter/glutamate metabolism (astrocytic glutamine synthetase), and connective-tissue/bone matrix synthesis (e.g., glycosyltransferases). At excessive exposures it can accumulate in the basal

ergothioneine

Pathway_overlap

Gene: CPT2

ergothioneine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Ergothioneine (EGT) is a diet-derived, sulfur-containing histidine derivative that is selectively transported into cells by OCTN1 (SLC22A4) and accumulates in stress-exposed tissues and subcellular compartments (notably mitochondria and nucleus). It acts mainly as a cytoprotective redox buffer—directly scavenging reactive oxygen/nitrogen species, chelating

ganglia/mitochondria, disturb dopaminergic signaling and energy metabolism, and promote oxidative stress, apoptosis and ferroptosis.

Recommendation: monitor

redox-active metals, and supporting endogenous antioxidant systems (including glutathione) while down-modulating inflammatory and pro-fibrotic signaling and, in some models, enhancing autophagy/mitochondrial integrity.

Recommendation: monitor

phosphatidylserine

Pathway_overlap

Gene: CPT2

phosphatidylserine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Phosphatidylserine (PS) is an anionic membrane phospholipid enriched on the cytosolic leaflet, especially in brain. As a supplement it supplies exogenous PS (historically bovine cortex; now mainly soy/sunflower), which can be incorporated into lipoproteins/cell membranes and influence membrane-dependent signaling. Endogenous PS provides a required electrostatic platform for recruitment/activation of signaling proteins (e.g., Akt/PKB, Raf-1, PKC) and supports synaptic vesicle fusion and receptor function; when externalized to the outer leaflet it acts as an "eat-me" signal that engages PS receptors on immune cells and can modulate inflammation/coagulation.

Recommendation: monitor

shilajit

Pathway_overlap

Gene: CPT2

shilajit affects a pathway related to CPT2. Monitor for effects.

Mechanism: Shilajit is a complex herbo-mineral exudate rich in fulvic/humic substances and dibenzo-α-pyrones that appears to act as a pleiotropic adaptogen: it can modulate stress signaling (HPA axis), support mitochondrial bioenergetics, exert antioxidant/anti-inflammatory effects (e.g., NF-κB/AKT/caspase signaling in preclinical liver injury), and may have direct antiviral effects in vitro likely via interference with viral attachment/entry or replication and host redox/immune modulation. Neuroactive effects reported in mouse slice electrophysiology suggest glycine_receptor and GABA_A_receptor agonist/positive modulatory activity, which could contribute to sedative/analgesic or autonomic/endocrine effects.

Recommendation: monitor

nac

Pathway_overlap

Gene: CPT2

nac affects a pathway related to CPT2. Monitor for effects.

Mechanism: N-acetyl-L-cysteine (NAC) is a cysteine prodrug that increases intracellular cysteine availability to support glutathione (GSH) synthesis and thiol redox buffering; it can also reduce/disrupt disulfide bonds in mucins (mucolytic) and modulate redox-sensitive signaling and inflammation. Direct ROS scavenging occurs for some oxidants but is often over-attributed; many observed effects reflect restored thiol/GSH pools, altered probe chemistry, and changes in mitochondrial redox state rather than broad, fast ROS neutralization.

Recommendation: monitor

creatine

Pathway_overlap

Gene: CPT2

creatine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Creatine (most commonly creatine monohydrate) increases tissue creatine and phosphocreatine stores, enhancing the creatine kinase (CK) phosphagen system to buffer ATP/ADP during high-energy demand. This supports repeated high-intensity work, increases training volume, promotes cell hydration/osmosensing and downstream anabolic signaling, and may support mitochondrial function, neuroprotection, and cardiac energetics in energy-stressed states.

Recommendation: monitor

iron

Pathway_overlap

Gene: CPT2

iron affects a pathway related to CPT2. Monitor for effects.

Mechanism: Iron is an essential trace mineral that supports oxygen transport and cellular energy metabolism by serving as a cofactor in hemoglobin/myoglobin and in iron–sulfur (Fe–S) proteins and heme enzymes of mitochondrial respiration. It is tightly regulated via intestinal absorption and systemic iron trafficking (hepcidin–ferroportin axis); deficiency limits erythropoiesis and oxidative phosphorylation, while excess promotes reactive oxygen species (ROS) generation and can drive lipid peroxidation/ferroptosis.

Recommendation: monitor

glycine

Pathway_overlap

Gene: CPT2

glycine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Glycine is a conditionally essential amino acid that (1) acts as an inhibitory neurotransmitter via glycine-gated chloride channels and as an obligatory co-agonist at NMDA receptors, modulating neuronal excitability and sleep; (2) serves as a major substrate for collagen synthesis and as a precursor for glutathione, creatine, heme and purines; and (3) participates in one-carbon metabolism through serine↔glycine interconversion and the glycine cleavage system, influencing methyl-group availability and redox balance.

Recommendation: monitor

nutritional-yeast

Pathway_overlap

Gene: CPT2

nutritional-yeast affects a pathway related to CPT2. Monitor for effects.

Mechanism: Nutritional yeast (typically deactivated Saccharomyces cerevisiae; sometimes other yeasts) is a nutrient-dense food supplement providing complete protein, B vitamins (often fortified with B12), minerals, beta-glucans and mannan-oligosaccharides (MOS) from the cell wall. Its benefits derive from micronutrient repletion and from cell-wall polysaccharides that can modulate gut microbiota and mucosal/innate immune responses and bind certain microbial toxins/pathogens.

Recommendation: monitor

cobalamin

Pathway_overlap

Gene: CPT2

cobalamin affects a pathway related to CPT2. Monitor for effects.

Mechanism: Cobalamin (vitamin B12) is an essential water-soluble vitamin that functions as an obligate cofactor for two human enzymes: methionine synthase (cytosolic, methylcobalamin) and methylmalonyl-CoA mutase (mitochondrial, adenosylcobalamin). Through these reactions it supports one-carbon metabolism (methionine/SAM production, DNA/RNA methylation) and mitochondrial odd-chain fatty acid and branched-chain amino acid catabolism (conversion of methylmalonyl-CoA to succinyl-CoA), thereby influencing hematopoiesis, myelin maintenance, and neurologic function; it also exhibits context-dependent redox activity (antioxidant/anti-inflammatory, but potentially pro-oxidant when combined with strong reducing agents in vitro/experimental settings).

Recommendation: monitor

borage-oil

Pathway_overlap

Gene: CPT2

borage-oil affects a pathway related to CPT2. Monitor for effects.

Mechanism: Borage oil is a botanical oil rich in gamma-linolenic acid (GLA, 18:3 n-6) and linoleic acid

magnesium

Pathway_overlap

Gene: CPT2

magnesium affects a pathway related to CPT2. Monitor for effects.

Mechanism: Magnesium (Mg2+) is an essential intracellular cation that stabilizes ATP (Mg-ATP) and

(LA, 18:2 n-6). GLA is elongated to dihomo-gamma-linolenic acid (DGLA), which can increase anti-inflammatory eicosanoids (e.g., PGE1) and compete with arachidonic acid for cyclooxygenase/lipoxygenase enzymes, often lowering pro-inflammatory leukotriene signaling; in skin it supports epidermal lipid synthesis (acyl-ceramides/corneocyte lipid envelope) and barrier repair.

Recommendation: monitor

functions as a cofactor for hundreds of enzymes. Physiologically it modulates excitability by regulating ion channels (including voltage-gated Ca2+ channels) and acting as a voltage-dependent, non-competitive blocker of NMDA receptor channels, and it supports neuromuscular, cardiovascular, metabolic, and mitochondrial functions; intestinal (TRPM6/7) and renal handling tightly control serum Mg2+.

Recommendation: monitor

molybdenum

Pathway_overlap

Gene: CPT2

molybdenum affects a pathway related to CPT2. Monitor for effects.

Mechanism: Molybdenum is an essential trace transition metal incorporated into the molybdenum cofactor (Moco), which enables human molybdoenzymes—primarily sulfite oxidase, xanthine oxidoreductase (xanthine oxidase/dehydrogenase), aldehyde oxidase, and mitochondrial amidoxime reducing component (mARC)—to catalyze key oxygen-atom transfer and redox reactions in sulfur amino acid metabolism, purine catabolism/uric acid formation, and metabolism of aldehydes and certain drugs/xenobiotics.

Recommendation: monitor

emoxypine

Pathway_overlap

Gene: CPT2

emoxypine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Emoxypine (2-ethyl-6-methyl-3-hydroxypyridine) and the related prescription drug emoxypine succinate/Mexidol act primarily as antioxidant/membrane-protective and antihypoxic neuroprotectants. They can scavenge reactive oxygen species, reduce lipid peroxidation, modulate glutamatergic excitotoxicity (including NMDA-related signaling) and GABAergic tone, and—when provided as the succinate salt—serve as a succinate donor supporting mitochondrial complex II (succinate dehydrogenase) respiration, improving ATP generation under hypoxia/ischemia; succinate may also signal via SUCNR1 to influence stress-response and mitochondrial biogenesis programs.

Recommendation: monitor

resistant-maltodextrin

Pathway_overlap

Gene: CPT2

resistant-maltodextrin affects a pathway related to CPT2. Monitor for effects.

Mechanism: Resistant maltodextrin (RMD; e.g., Fibersol-2) is a digestion-resistant, soluble, low-viscosity fermentable fiber that escapes small-intestinal digestion, slows carbohydrate absorption modestly, and is fermented by colonic microbiota to short-chain fatty acids (SCFAs) that support gut barrier function and incretin (GLP-1/PYY) signaling, improving postprandial glycemia, bowel habits, and some cardiometabolic risk markers.

Recommendation: monitor

histidine

Pathway_overlap

Gene: CPT2

histidine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Histidine is an essential amino acid used for protein synthesis and as a precursor to histamine (via histidine decarboxylase) and to the dipeptide carnosine (β-alanyl-L-histidine). Through histamine and carnosine/imidazole chemistry, histidine availability can influence gastric acid secretion, neurotransmission/immune signaling, metal ion binding/buffering, and antioxidant/anti-glycation defense; a related dietary histidine derivative, ergothioneine, is transported via OCTN1 and

accumulates in mitochondria/nucleus to quench reactive species and support glutathione redox cycling.

Recommendation: monitor

niacin

Pathway_overlap

Gene: CPT2

niacin affects a pathway related to CPT2. Monitor for effects.

Mechanism: Niacin (nicotinic acid, vitamin B3) is a precursor of NAD+/NADP+ supporting redox metabolism and as a pharmacologic agent activates the GPCR GPR109A (HM74A) on adipocytes and immune/skin cells, altering lipolysis, hepatic VLDL assembly, HDL/apoA-I kinetics, and inflammatory signaling; its common adverse flushing is driven by GPR109A-mediated prostaglandin release in skin.

Recommendation: monitor

5mg-lithium-orotate

Pathway_overlap

Gene: CPT2

5mg-lithium-orotate affects a pathway related to CPT2. Monitor for effects.

Mechanism: Lithium orotate provides low-dose elemental lithium complexed to orotic acid; lithium ions modulate neuronal and cellular signaling (notably inhibiting inositol monophosphatase and glycogen synthase kinase-3), influencing neurotransmission, neurotrophic signaling, circadian regulation, and inflammatory/oxidative stress responses. Compared with prescription lithium salts, lithium orotate is marketed for OTC microdosing, but robust human clinical evidence for benefits at 5 mg is limited and safety monitoring principles for lithium still apply (renal/thyroid).

Recommendation: monitor

copper

Pathway_overlap

Gene: CPT2

copper affects a pathway related to CPT2. Monitor for effects.

Mechanism: Copper is an essential redox-active trace mineral that cycles between Cu(I)/Cu(II) and is delivered to specific cuproenzymes by intracellular copper chaperones (e.g., ATOX1→ATP7A/ATP7B; CCS→SOD1; COX17/COX11/SCO1/2→cytochrome c oxidase). Through these enzymes copper supports mitochondrial respiration, antioxidant defense, connective-tissue crosslinking, catecholamine synthesis, and iron mobilization; excess unbound copper can catalyze oxidative damage and, in mitochondria, trigger copper-dependent regulated cell death (cuproptosis) via binding to lipoylated TCA-cycle proteins.

Recommendation: monitor

allicin

Pathway_overlap

Gene: CPT2

allicin affects a pathway related to CPT2. Monitor for effects.

Mechanism: Allicin (diallylthiosulfinate) is a reactive sulfur species generated from alliin by alliinase when garlic is crushed. It exerts many effects by S-thioallylation/oxidation of protein and glutathione thiols, altering redox signaling and enzyme activity; downstream, it can enhance endothelial vasodilatory signaling, modulate inflammatory transcription programs, and trigger antimicrobial stress responses in microbes.

Recommendation: monitor

akkermansia

Pathway_overlap

Gene: CPT2

vitamin-k2

Pathway_overlap

Gene: CPT2

akkermansia affects a pathway related to CPT2. Monitor for effects.

Mechanism: Akkermansia muciniphila is a mucin-degrading, mucus-layer–resident gut bacterium that can improve metabolic and inflammatory phenotypes by strengthening the intestinal barrier (increasing mucus thickness and tight-junction function), altering gut immune tone, and producing/inducing metabolites (e.g., short-chain fatty acids and secondary bile acids) that signal through host receptors (e.g., TLR2, FXR/TGR5) to modulate glucose, lipid and immune pathways. Both live and pasteurized Akkermansia and specific outer-membrane proteins/EVs have shown activity in preclinical models, with human proof-of-concept data suggesting improvements in insulin sensitivity and some cardiometabolic markers in overweight/insulin-resistant adults.

Recommendation: monitor

vitamin-k2

Pathway_overlap

Gene: CPT2

vitamin-k2 affects a pathway related to CPT2. Monitor for effects.

Mechanism: Vitamin K2 (menaquinones; commonly MK-4 or MK-7) serves as a cofactor for γ-glutamyl carboxylase, enabling activation (γ-carboxylation) of vitamin K–dependent proteins such as osteocalcin and matrix Gla protein (MGP), which regulate calcium handling in bone and vasculature. K2 also has non-canonical actions including nuclear receptor activation (SXR/PXR), anti-inflammatory signaling (e.g., NF-κB suppression), and antioxidant/anti-ferroptotic effects linked to GPX4 and redox control in certain models.

Recommendation: monitor

flax-oil

Pathway_overlap

Gene: CPT2

flax-oil affects a pathway related to CPT2. Monitor for effects.

Mechanism: Flax oil is rich in the omega-3 fatty acid alpha-linolenic acid (ALA), which incorporates into cell membranes and is enzymatically converted (limited in humans) to EPA/DHA, shifting eicosanoid/oxylipin signaling toward less pro-inflammatory mediators. Preclinical data show modulation of hepatic lipid metabolism via PPAR signaling (notably PPAR-γ and likely PPAR-α), reducing lipogenesis and hepatic lipid accumulation and improving lipid profiles and oxidative/inflammatory status.

Recommendation: monitor

hydroxytyrosol

Pathway_overlap

Gene: CPT2

hydroxytyrosol affects a pathway related to CPT2. Monitor for effects.

Mechanism: Hydroxytyrosol (HT; 3,4-dihydroxyphenylethanol) is an olive-derived phenolic that acts as a redox-active cytoprotective and anti-inflammatory agent: it scavenges reactive species and more importantly activates endogenous antioxidant defenses (e.g., Nrf2) while dampening pro-inflammatory signaling (e.g., NF-κB/iNOS/COX-2) and improving vascular and lipid biology, which together can reduce oxidative damage to lipids (including LDL) and tissues.

Recommendation: monitor

spirulina/chlorella

Pathway_overlap

Gene: CPT2

spirulina/chlorella affects a pathway related to CPT2. Monitor for effects.

Mechanism: Spirulina (a cyanobacterium) and chlorella (a green microalga) are nutrient-dense biomass sources rich in proteins, carotenoids, phycobiliproteins (spirulina), chlorophyll and chlorophyll-derivatives (chlorella), polysaccharides and peptides. Their reported benefits are attributed to antioxidant and anti-inflammatory activity, modulation of innate/adaptive

vitamin-c

Pathway_overlap

Gene: CPT2

vitamin-c affects a pathway related to CPT2. Monitor for effects.

Mechanism: Vitamin C (ascorbic acid/ascorbate) is a water-soluble redox molecule that donates electrons to neutralize reactive oxygen/nitrogen species and to regenerate other antioxidants (e.g., vitamin E). It also acts as an essential cofactor for Fe2+/2-oxoglutarate–dependent dioxygenases (collagen prolyl/lysyl hydroxylases, HIF prolyl hydroxylases, and TET/JmjC

immune signaling, gut microbiota effects from polysaccharides/fiber-like fractions, and metabolic effects on lipid/glucose handling; some constituents (e.g., chlorophyllin, carotenoids, phycocyanin) can also bind/react with reactive intermediates and influence xenobiotic-metabolizing enzymes.

Recommendation: monitor

enzymes), influencing connective-tissue integrity, vascular function, hypoxia signaling, and epigenetic regulation; at pharmacologic (especially IV) doses it can become pro-oxidant in the presence of catalytic metals, generating extracellular H2O2 that may preferentially stress cancer cells.

Recommendation: monitor

folate

Pathway_overlap

Gene: CPT2

folate affects a pathway related to CPT2. Monitor for effects.

Mechanism: Folate (vitamin B9) is converted to tetrahydrofolate (THF) cofactors that carry one-carbon units for nucleotide synthesis (purines and thymidylate), methylation reactions via methionine/S-adenosylmethionine, and amino-acid interconversions (serine↔glycine). Adequate folate supports DNA synthesis/repair, red blood cell production, and homocysteine remethylation; deficiency impairs cell division and causes megaloblastic anemia and increases neural tube defect risk.

Recommendation: monitor

l.-acidophilus-ncfm

Pathway_overlap

Gene: CPT2

l.-acidophilus-ncfm affects a pathway related to CPT2. Monitor for effects.

Mechanism: Lactobacillus acidophilus NCFM is a human-derived probiotic strain that transiently colonizes the gut, interacts with intestinal epithelium via surface layer proteins and adhesion factors, and modulates mucosal and systemic immunity (including enhancing regulatory T-cell function) while influencing microbiota metabolic output (e.g., short-chain fatty acids) through carbohydrate fermentation and cross-feeding.

Recommendation: monitor

l-norvaline

Pathway_overlap

Gene: CPT2

l-norvaline affects a pathway related to CPT2. Monitor for effects.

Mechanism: L-norvaline is a non-proteinogenic branched-chain amino acid that primarily acts as an arginase (ARG1/ARG2) inhibitor, potentially increasing L-arginine availability for nitric_oxide_synthase (NOS) and modulating urea_cycle flux. It has also been reported (mainly in animal/cell models) to inhibit S6K1 (a downstream effector of mTORC1), linking it to reduced inflammatory/oxidative signaling; however, in vitro data suggest it can cause mitochondrial dysfunction and cytotoxicity at relatively low micromolar concentrations, likely via off-target metabolic interference and/or misincorporation-related toxicity typical of some non-proteinogenic amino acids.

Recommendation: monitor

carob

Pathway_overlap

Gene: CPT2

carob affects a pathway related to CPT2. Monitor for effects.

Mechanism: Carob (Ceratonia siliqua) provides (1) insoluble/soluble fibers (carob bean gum/galactomannans) that increase viscosity, bind bile acids and slow glucose absorption; and (2) polyphenols (e.g., proanthocyanidins, gallic acid derivatives) and inositols (notably D-pinitol) that modulate oxidative stress/inflammation and improve insulin signaling. Leaf extracts also show endothelium-dependent vasorelaxation likely via nitric-oxide signaling and/or calcium channel modulation in vascular smooth muscle.

Recommendation: monitor

broccoli-seed-extract/sulforaphane-liposomal

Pathway_overlap

Gene: CPT2

broccoli-seed-extract/sulforaphane-liposomal affects a pathway related to CPT2. Monitor for effects.

Mechanism: Broccoli seed extract provides glucoraphanin and/or preformed sulforaphane; sulforaphane is an electrophilic isothiocyanate that activates Nrf2 by modifying Keap1 cysteines, inducing phase II cytoprotective and antioxidant enzymes, while also modulating NF-κB–driven inflammation, mitochondrial/redox status, and gut barrier/microbiome interactions. Liposomal formulations aim to improve sulforaphane stability and absorption versus conventional oral preparations.

Recommendation: monitor

l-fermentum

Pathway_overlap

Gene: CPT2

l-fermentum affects a pathway related to CPT2. Monitor for effects.

Mechanism: Limosilactobacillus (Lactobacillus) fermentum is a lactic-acid–producing probiotic whose benefits are strain-specific and largely mediated by (1) modulation of gut microbiota and barrier/immune signaling, (2) production or biotransformation of bioactive metabolites (e.g., ferulic acid release/production; GABA in fermented substrates), and (3) effects on bile acid handling and cholesterol metabolism (assimilation, bile salt hydrolase activity, and interference with intestinal cholesterol uptake).

Recommendation: monitor

thiamine

Pathway_overlap

Gene: CPT2

thiamine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Thiamine (vitamin B1) is converted to thiamine diphosphate/pyrophosphate (ThDP/TPP), an essential coenzyme for key carbohydrate and branched-chain amino acid oxidation enzymes (e.g., pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, transketolase, branched-chain α-ketoacid dehydrogenase), thereby supporting ATP production, neurotransmitter synthesis, and redox balance. Beyond coenzyme roles, thiamine and phosphorylated forms (e.g., ThTP) appear to modulate neuronal excitability and cholinergic signaling and may influence inflammation and pain pathways.

Recommendation: monitor

vitamin-e

Pathway_overlap

Gene: CPT2

vitamin-e affects a pathway related to CPT2. Monitor for effects.

Mechanism: Vitamin E is a family of lipophilic tocopherols/tocotrienols (dietary requirement is primarily α-tocopherol) that acts as a chain-breaking, radical-trapping antioxidant in membranes and lipoproteins, terminating lipid peroxidation and supporting membrane integrity. Beyond antioxidant activity, α-tocopherol and certain vitamin E metabolites/derivatives (e.g., tocopheryl phosphate/succinate) modulate gene expression and signaling (inflammation, cell survival/apoptosis, lipid handling) and are selectively trafficked/regulated by hepatic α-tocopherol transfer protein (α-TTP), lipoprotein pathways, and transporters (e.g., SR-BI, ABCA/ABCG), including in the CNS.

Recommendation: monitor

epicatechin

Pathway_overlap

Gene: CPT2

epicatechin affects a pathway related to CPT2. Monitor for effects.

black-seed/thymoquinone

Pathway_overlap

Gene: CPT2

black-seed/thymoquinone affects a pathway related to CPT2. Monitor for effects.

Mechanism: Epicatechin is a flavan-3-ol polyphenol that modulates redox and inflammatory signaling rather than acting as a direct "vitamin-like" antioxidant; it can activate endogenous antioxidant defenses (e.g., Nrf2/HO-1), improve endothelial nitric-oxide bioavailability, and influence pro-survival/neuroplasticity pathways (PI3K/Akt, ERK/CREB), thereby reducing oxidative stress, inflammation, and apoptosis. Some derivatives (e.g., epicatechin gallate) can also inhibit enzymes such as xanthine oxidase and may interfere with amyloid/tau aggregation processes in neurodegeneration models.

Recommendation: monitor

Mechanism: Black seed (Nigella sativa) preparations—especially thymoquinone (TQ)–rich oil—act as pleiotropic redox and inflammation modulators. TQ can activate antioxidant defense (notably via Nrf2/ARE signaling), suppress pro-inflammatory transcription (e.g., NF-κB/STAT3), and influence metabolic signaling (e.g., PI3K/AKT/AMPK), leading to improved oxidative stress handling, lower inflammatory tone, and in some settings improved insulin sensitivity and dysregulated cell growth control.

Recommendation: monitor

400mg-rhodiola

Pathway_overlap

Gene: CPT2

400mg-rhodiola affects a pathway related to CPT2. Monitor for effects.

Mechanism: Rhodiola rosea is an adaptogenic herb whose phenylpropanoids (rosavins) and salidroside appear to modulate stress-response systems (HPA axis and sympathetic signaling), influence monoamine neurotransmission (serotonin, dopamine, norepinephrine), and reduce stress-related fatigue, potentially via mild MAO/COMT modulation, neuroprotective antioxidant effects, and improved cellular energy metabolism under stress.

Recommendation: monitor

astragaloside-iv

Pathway_overlap

Gene: CPT2

astragaloside-iv affects a pathway related to CPT2. Monitor for effects.

Mechanism: Astragaloside IV (AS-IV) is a cycloartane-type triterpenoid saponin from Astragalus membranaceus that acts as a pleiotropic cytoprotective and immunomodulatory agent. Across preclinical models it reduces oxidative and inflammatory injury, stabilizes mitochondrial function, and limits regulated cell-death programs (notably pyroptosis and ferroptosis) via modulation of AMPK/SIRT1, NF-κB, PI3K/AKT, and redox-sensing pathways.

Recommendation: monitor

taurine

Pathway_overlap

Gene: CPT2

taurine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Taurine (2-aminoethanesulfonic acid) is a sulfur-containing, non-proteinogenic amino acid that acts primarily as an osmolyte and cytoprotective signaling molecule. It conjugates bile acids (taurocholate), modulates intracellular Ca2+ handling and ion channel activity, stabilizes membranes/mitochondria, and reduces inflammation and oxidative injury (partly via supporting glutathione status and forming taurine chloramine that dampens NF-κB-driven cytokines).

Recommendation: monitor

uridine-monophosphate

Pathway_overlap

Gene: CPT2

uridine-monophosphate affects a pathway related to CPT2. Monitor for effects.

Mechanism: Uridine monophosphate (UMP) is a pyrimidine nucleotide that can be dephosphorylated to uridine and absorbed, then salvaged back to UMP/UTP/CTP for RNA synthesis, glycogen and lipid metabolism (via UDP-sugars), and phospholipid synthesis (Kennedy pathway). Exogenous uridine/UMP can bypass or partially rescue blocks in de novo pyrimidine synthesis (e.g., DHODH inhibition by leflunomide/teriflunomide), supporting proliferating cells and modulating immune cell function; in the CNS it may support synaptic membrane phosphatide synthesis when combined with choline and DHA.

Recommendation: monitor

beta-alanine

Pathway_overlap

Gene: CPT2

beta-alanine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Beta-alanine is the rate-limiting precursor for synthesis of the dipeptide carnosine in skeletal muscle; higher intramuscular carnosine increases intracellular buffering of H+ during high-intensity exercise, helping maintain contractile function and delaying fatigue. Carnosine may also modulate calcium handling/sensitivity and act as an antioxidant/carbonyl scavenger; beta-alanine also crosses the blood–brain barrier and has been reported ex vivo to exert multi-target neuroprotective effects under ischemia-like conditions.

Recommendation: monitor

vanadium

Pathway_overlap

Gene: CPT2

vanadium affects a pathway related to CPT2. Monitor for effects.

Mechanism: Vanadium (commonly as vanadyl/vanadate) is a redox-active trace metal whose oxyanions resemble phosphate, allowing it to inhibit/alter phosphatase and ATPase reactions; in mammals this can enhance insulin signaling (insulin-mimetic/insulin-sensitizing) largely via protein tyrosine phosphatase inhibition, while many vanadium complexes also induce reactive oxygen species (ROS) and mitochondrial stress that can trigger cell-cycle arrest and apoptosis (basis for experimental anticancer/antiparasitic activity).

Recommendation: monitor

rapamycin

Pathway_overlap

Gene: CPT2

rapamycin affects a pathway related to CPT2. Monitor for effects.

Mechanism: Rapamycin (sirolimus) is a macrolide that binds FKBP12 to form a complex that allosterically inhibits mTORC1, suppressing cap-dependent translation, cell-cycle progression (G1/S), and anabolic metabolism while promoting autophagy; with chronic exposure it can also impair mTORC2 assembly in some tissues, affecting insulin/AKT signaling. These effects underlie immunosuppression (reduced IL-2–driven lymphocyte proliferation) and broad impacts on growth, metabolism, and aging-related pathways.

Recommendation: monitor

inosine

Pathway_overlap

Gene: CPT2

inosine affects a pathway related to CPT2. Monitor for effects.

Mechanism: Inosine is a purine nucleoside that can be taken up by cells and converted (via purine salvage) to inosine monophosphate (IMP), supporting ATP/GTP pools and potentially aiding energy metabolism under stress. Extracellular inosine can also act as an immunometabolite and signaling molecule via adenosine receptors (after conversion to hypoxanthine/adenosine or direct receptor activity in some contexts), modulating inflammation (e.g., PPARγ activation in colitis models) and thermogenic programs (e.g., brown adipose signaling).

Recommendation: monitor

doxepin

Pathway_overlap

Gene: CPT2

doxepin affects a pathway related to CPT2. Monitor for effects.

astragalus

Pathway_overlap

Gene: CPT2

astragalus affects a pathway related to CPT2. Monitor for effects.

Mechanism: Doxepin is a tricyclic antidepressant (TCA) whose clinical effects depend strongly on dose: at very low doses it is a highly potent histamine H1 receptor antagonist producing sleep-maintenance sedation; at higher antidepressant doses it additionally inhibits serotonin and norepinephrine reuptake and antagonizes multiple receptors (H1/H2, muscarinic, alpha1-adrenergic), explaining both efficacy and anticholinergic/orthostatic adverse effects. It is hepatically metabolized (notably via CYP2D6 with contributions from CYP3A4 and CYP1A enzymes) to active metabolites (e.g., nordoxepin) and undergoes conjugation (including N+-glucuronidation).

Recommendation: monitor

Mechanism: Astragalus (Astragalus membranaceus/mongholicus; "Huangqi") contains immunomodulatory polysaccharides (APS) and triterpenoid saponins (notably astragaloside IV) that act as pleiotropic regulators of innate/adaptive immunity, oxidative stress and endothelial function. Across preclinical models, APS/AS-IV reduce inflammatory signaling (e.g., TLR4→NF-κB), modulate macrophage and T-cell polarization, improve insulin sensitivity and mitochondrial/vascular function, and can shift gut microbiota toward SCFA-producing taxa—collectively supporting metabolic, cardio-renal and mucosal barrier protection.

Recommendation: monitor

▼ No Concerns Found (97 supplements)

eleuthero, b-breve, hyaluronic-acid, l.-rhamnosus-gg, ezetimibe, c.-butyricum-miyairi, acarbose, lutein-and-zeaxanthin, 10mg-zinc, dgl, hmo, tongkat-ali, bromelain, b.-lactis-bb12, b.-lactis-hn019, calcium-carbonate, anserine, glucosamine-sulfate, b-clausii, s.-boulardii-cncm-i-745, tryptophan, glucomannan, psyllium-husk, inulin, muvalaplin, ldn, dextrose, b-longum, beta-glucans, b.-longum ...

Gene Deep Dives

Detailed reports for each of your gene variants.

CPT2 — Full Report

1. Variant Information

Gene	CPT2
Variant ID	rs74315294
Protein Change	p.Ser113Leu
Genotype	C/T
ClinVar Classification	Pathogenic

Pathogenicity Score	45
Predicted Phenotype	Carrier or possibly affected

2. Associated Diseases

Severe illness energy-crisis sensitivity

During a major infection with fever, the body can shift into a high 'fuel-demand' state. If fat-to-energy processing can't keep up, some people can develop serious metabolic instability that can affect the brain and body.

For carriers: Classic severe episodes are mainly documented in people with CPT2 deficiency affecting both gene copies. For heterozygous carriers, severe infection/fever can still be an important stressor because symptomatic carriers have been reported, but how often carriers develop brain-involved illness episodes is not documented in the reviewed literature.

3. Variant Mechanism

CPT2 is part of your cells' "fat-to-energy" system. Think of long-chain fats as big fuel logs that can't be burned until they're carried into the cell's power plant (the mitochondria). CPT2 is one of the key enzymes that helps move these long-chain fats into the mitochondria so they can be broken down for energy (especially when you're fasting, sick, or exercising for a long time). With a pathogenic CPT2 variant, that fat-burning step can be less efficient—so in high-demand situations your muscles (and sometimes other organs) may run short on usable energy and build up partially processed fat byproducts (acylcarnitines) that can irritate tissues.

Evidence Summary: Most people with classic CPT2 deficiency have two affected copies (autosomal recessive). However, the reviewed literature shows that some heterozygous carriers can still have symptoms—typically muscle pain, weakness, cramps, or even rhabdomyolysis—especially under strong stressors like prolonged/intense exercise, fever/illness, or fasting. This seems to happen when the remaining working copy doesn't fully cover increased energy needs or when other factors (genetic modifiers, environment) further reduce fat-oxidation capacity. Evidence comes from symptomatic heterozygous case reports and larger patient series noting probable symptomatic carriers.

4. Carrier Phenotype

With one pathogenic CPT2 variant (heterozygous carrier), many people feel completely well. That said, the reviewed literature shows that a small number of carriers can have 'classic' CPT2-type muscle symptoms—especially when they push their metabolism hard (endurance exercise, overheating/fever, or fasting). If symptoms happen, they tend to look like exercise-induced muscle pain/burning, cramps, weakness, or in rare cases rhabdomyolysis (muscle breakdown). The best way to think about it is: you likely have a safety margin most of the time, but your margin may shrink under stress.

Can be symptomatic: Yes

Symptom frequency: Unclear; reported but appears uncommon based on limited carrier-focused data.

5. Documented Triggers

Prolonged fasting / overnight fasting (2020)

Fasting forces the body to rely more on long-chain fat burning. In long-chain FAODs including CPT2 deficiency, disease-specific long-chain acylcarnitines were higher after an overnight fast and fell after feeding, showing fasting pushes metabolism toward the vulnerable pathway. Review articles also list prolonged fasting as a common trigger for decompensation.

Infection / fever / inflammatory illness (2019)

Illness and fever increase energy needs and push the body into a more catabolic state (breaking down stored fuels). Reviews of long-chain FAODs list infection as a common trigger for hypoglycemia, rhabdomyolysis, and organ stress. A symptomatic heterozygous athlete had rhabdomyolysis after extensive exercise plus fever from heat exposure, highlighting that fever can 'tip the balance' even in carriers. Anesthesia case report also shows severe hyperthermia-like stress can be relevant in a heterozygous CPT2 mutation carrier.

Strenuous or prolonged exercise (especially endurance) (2012)

Long, hard exercise increases reliance on fat oxidation. Adult/muscle CPT2 deficiency is classically triggered by prolonged exercise and can cause rhabdomyolysis. Feeding studies show moderate-intensity exercise can raise disease-specific acylcarnitines in long-chain FAODs, reflecting metabolic stress. Symptomatic heterozygous carriers have been reported in endurance athletes with exercise-induced myalgia/weakness and rhabdomyolysis.

Cold exposure (2003)

Cold is listed as a trigger for myoglobinuria episodes in CPT II deficiency in a review of metabolic exercise intolerance, likely because shivering and thermogenesis raise energy demand and can increase reliance on fat oxidation.

Heat stress / insolation (overheating) especially with exercise (2012)

A symptomatic heterozygous marathon runner developed rhabdomyolysis with extensive exercise plus insolation-induced fever, suggesting overheating is a meaningful amplifier of risk in carriers.

High-fat meal (fat-rich meal) (2025)

A case-based review on CPT2 deficiency notes attacks are commonly triggered by consumption of a fat-rich meal, which can increase reliance on long-chain fat processing—exactly the step CPT2 supports.

6. Evidence-Based Recommendations

Lifestyle

Treat sleep and recovery as part of your 'energy budget'—aim for consistent sleep and build in recovery days after hard workouts.

REVIEW

Have an 'illness plan' for fevers: prioritize early fluids and carbs, and lower activity until fully recovered.

CASE REPORT N=2

Be cautious with extreme temperatures during exercise (very hot or very cold days).

Diet

COHORT 25 CITES N=30

Don't do long fasts: aim to eat within 1–2 hours of waking, then every ~3–4 hours while awake (more often if you're active or unwell).

RCT N=11

Before endurance-style exercise, take in carbohydrates (and consider discussing MCT with your metabolic team if you ever develop clear CPT2-type symptoms).

CASE REPORT 1 CITES N=1

If you notice symptoms after very fatty meals, experiment with balancing meals toward carbs + protein and keeping high-fat meals smaller and earlier in the day.

Exercise

CASE REPORT N=2

Favor 'steady, moderate' over 'all-out': build intensity gradually, and stop early if you get deep muscle burning, unusual weakness, or cramping.

CASE REPORT N=2

Avoid combining long endurance sessions with overheating or fever; reschedule hard workouts when sick or in extreme heat.

COHORT 2 CITES N=27

Supplements

REVIEW

L-carnitine: Only consider supplementation after discussing with a clinician familiar with fatty-acid oxidation disorders. It may be considered in CPT2 deficiency, especially if labs show low free carnitine; it's not something I'd start blindly as a carrier. *(Dosage: Not documented in reviewed literature for carriers.)*

If you ever develop confirmed CPT2-related symptoms, ask about supervised exercise testing/monitoring strategies with a specialist team.

Pharmaceuticals

Important: Consult your doctor before starting any medication.

CASE SERIES N=6

Bezafibrate	(Fibrate (PPAR agonist))	If you ever develop confirmed CPT2 deficiency symptoms (recurrent rhabdomyolysis/exercise intolerance), bezafibrate is a medication to discuss with a metabolic specialist. It is not typically considered for asymptomatic carriers based on reviewed literature.	Side effects (moderate): Not detailed in the reviewed abstracts. As a fibrate, it can cause liver enzyme elevations, GI symptoms, and muscle-related side effects in some settings; discuss interactions and monitoring with a clinician.

Labs to Check

CASE REPORT N=2

Creatine kinase (CK) during/after concerning episodes: CK rises when muscle is injured. Because CPT2-related problems can present as rhabdomyolysis after triggers (exercise, fever), checking CK during symptoms helps confirm whether muscle breakdown is happening. *(Frequency: If you develop severe muscle pain/weakness, dark urine, or after an ER visit; routine screening in asymptomatic carriers is not documented in reviewed literature.)*

COHORT 25 CITES N=30

Plasma acylcarnitine profile (standardized conditions): Long-chain acylcarnitines can rise with fasting and exercise in CPT2 deficiency and may reflect metabolic stress. If measured, results depend heavily on whether you were fasting or recently ate/exercised, so standardized timing matters. *(Frequency: Only if a clinician is evaluating symptoms or monitoring known FAOD; routine monitoring for asymptomatic carriers is not documented in reviewed literature.)*

Symptoms to Watch

CASE REPORT N=2 SOON

Severe muscle pain/burning, cramps, or sudden weakness during or	These can be early signs that muscle energy supply is failing under stress, which is the classic pattern in CPT2-related muscle involvement—even	*Action: Stop the activity, cool down, drink fluids, and take in carbohydrates. If symptoms are unusual for you or don't improve quickly, seek medical evaluation and ask whether CK and urine*

Things to Avoid

COHORT 25 CITES N=30 Avoid

Prolonged fasting (including aggressive intermittent fasting)	(diet)	Fasting increases dependence on long-chain fat oxidation, which is the step supported by CPT2. In CPT2 deficiency, fasting raises long-chain acylcarnitines; feeding suppresses them.

after exercise	reported in symptomatic carriers.	*myoglobin should be checked.*

CASE SERIES | 54 CITES | N=25 | URGENT

Dark/cola-colored urine after exercise or illness	This can indicate myoglobinuria from rhabdomyolysis, which is a hallmark risk in CPT2 deficiency and has been reported in symptomatic heterozygotes under heavy stress.	*Action: Go to urgent care/ER the same day for evaluation (CK, kidney function) and hydration; mention CPT2 carrier status and concern for rhabdomyolysis.*

REVIEW | URGENT

High fever with profound fatigue, confusion, or inability to keep fluids down	Infection/fever is a major metabolic stressor in FAODs. Severe systemic symptoms can signal a developing metabolic crisis, especially if combined with poor intake (fasting).	*Action: Start frequent carbohydrate-containing fluids if tolerated and seek medical care promptly, especially if confusion or dehydration is present.*

CASE REPORT | N=2 | Strictly Avoid

Exercising hard when you have a fever or are overheating	(lifestyle)	Fever/infection and overheating raise energy demand and can combine with exercise to trigger rhabdomyolysis; this exact pattern is reported in a symptomatic heterozygous carrier.

CASE REPORT | 1 CITES | N=1 | Caution

Very fat-rich meals if you notice symptoms afterwards	(diet)	Fat-rich meals are cited as a trigger in CPT2 deficiency case-based literature; long-chain fat loads increase reliance on the CPT2-dependent pathway.

CASE REPORT | N=1 | Avoid

Succinylcholine and halothane anesthesia exposure without telling the anesthesia team your CPT2 status	(pharmaceutical)	A malignant hyperthermia-like episode was reported in a child heterozygous for a CPT2 mutation after succinylcholine and halothane. This is uncommon, but it's important for anesthesia planning and risk discussion.

REVIEW | 12 CITES | Caution

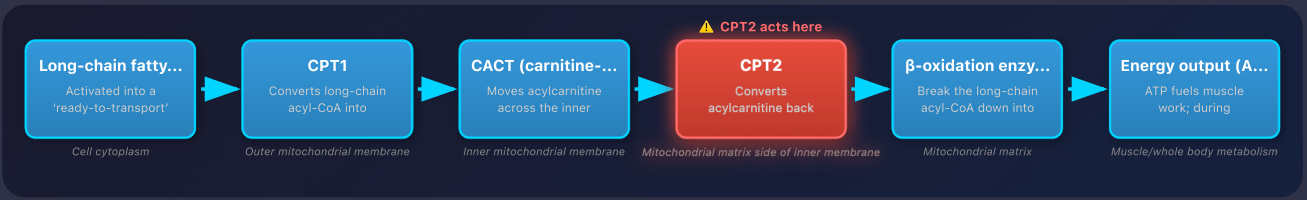
Extreme cold exposure during long exercise bouts	(lifestyle)	Cold is listed as a trigger for CPT II-associated myoglobinuria in metabolic exercise intolerance literature, likely by increasing energy demand (shivering/thermogenesis).

7. Key Biological Pathway

The Carnitine Shuttle (getting long-chain fats into mitochondria)

Why this matters: This is the central "fuel transport" pathway that explains both the symptoms and the triggers. When you're resting and eating regularly, your body can rely more on glucose. But during fasting, fever/infection, or long/intense exercise, your body leans heavily on long-chain fats. CPT2 is a key step in getting those fats into mitochondria to be burned for energy.

Your muscles store a lot of energy as fat, but long-chain fats need a special shuttle system to enter mitochondria, where energy is made. CPT2 is the step that turns the transported fat back into a form mitochondria can actually burn. If this step is sluggish, energy can drop right when your body needs it most, and fat byproducts can build up.



When this pathway is impaired:

When CPT2 doesn't work well, long-chain fats can't be efficiently converted into the 'burnable' form inside mitochondria. During catabolic stress (fasting, fever/infection, prolonged exercise), muscles may run short on energy and accumulate long-chain acylcarnitines—this combination can contribute to muscle pain/cramps, weakness, and in severe situations rhabdomyolysis (muscle breakdown). In diagnosed patients, long-chain acylcarnitines rise with fasting and often with exercise, and drop after feeding.

Other Related Pathways

Fatty acid degradation
KEGG: hsa00071
View Details →

Fatty acid metabolism
KEGG: hsa01212
View Details →

PPAR signaling pathway
KEGG: hsa03320
View Details →

Thermogenesis
KEGG: hsa04714
View Details →

Diabetic cardiomyopathy
KEGG: hsa05415
View Details →

Associated Conditions (KEGG)

- H00525 Disorders of mitochondrial fatty-acid oxidation
- H01400 Secondary hyperammonemia
- H01982 Carnitine palmitoyltransferase II deficiency
- H02536 Infection-induced acute encephalopathy
- H02596 Disorders of carnitine transport and the carnitine cycle

8. Emergency Protocol

If you develop a significant infection with fever, vomiting, or you're unable to eat normally, the goal is to avoid slipping into a fasting/catabolic state where your body leans heavily on long-chain fat burning (the CPT2-dependent pathway). Practical steps: (1) start sipping carbohydrate-containing fluids early (oral rehydration solution, juice, regular sports drink) and try small carb snacks frequently; (2) pause strenuous exercise until you're fully recovered; (3) keep warm/cool appropriately (avoid chills or overheating); (4) if you cannot keep fluids down, have dark urine, severe muscle pain/weakness, confusion, or persistent high fever, seek urgent medical care and tell the team you carry a pathogenic CPT2 variant and you're concerned about rhabdomyolysis/metabolic decompensation.

Warning Signs:

- Dark/cola urine
- Severe muscle pain or weakness
- Confusion or unusual sleepiness
- Persistent vomiting or inability to keep fluids down
- High fever plus rapid worsening fatigue

9. Protein Information

Protein Length	670 amino acids
Function	Involved in the intramitochondrial synthesis of acylcarnitines from accumulated acyl-CoA metabolites. Reconverts acylcarnitines back into the respective acyl-CoA esters that can then undergo beta-oxid

Subcellular Location	Mitochondrion inner membrane
Known Variants	0

10. Key References

Key References

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   Supports variant mechanism understanding
2. CASE SERIES 48 CITES N=49 **Allelic and phenotypic heterogeneity in 49 Italian patients with the muscle form of CPT-II deficiency.** (2012) PMID:21913903
   Supports variant mechanism understanding
3. CASE SERIES 54 CITES N=25 **Genotype-phenotype correlations in a large series of patients with muscle type CPT II deficiency.** (2011) PMID:20810031
   Supports variant mechanism understanding
4. REVIEW **Management and diagnosis of mitochondrial fatty acid oxidation disorders: focus on very-long-chain acyl-CoA dehydrogenase deficiency.** (2019) PMID:30401918
   Supports variant mechanism understanding
5. COHORT 25 CITES N=30 **Effects of fasting, feeding and exercise on plasma acylcarnitines among subjects with CPT2D, VLCADD and LCHADD/TFPD.** (2020) PMID:32928639
   Documents trigger: Prolonged fasting / overnight fasting
6. REVIEW 12 CITES **[Metabolic intolerance to exercise].** (2003) PMID:12838448
   Documents trigger: Cold exposure
7. CASE REPORT 1 CITES N=1 **Migratory and intermittent polyarthritis as an atypical presentation of carnitine palmitoyltransferase II deficiency with positive response to treatment with Interleukin-1 receptor antagonist: a case presentation and case-based review.** (2025) PMID:40580346
   Documents trigger: High-fat meal (fat-rich meal)
8. CASE REPORT N=1 **Malignant hyperthermia-like syndrome and carnitine palmitoyltransferase II deficiency with heterozygous R503C mutation.** (2009) PMID:19762733

Documents trigger: Certain anesthetics: succinylcholine and halothane (malignant hyperthermia-like episode)

9. RCT N=11 **Substrate oxidation and cardiac performance during exercise in disorders of long chain fatty acid oxidation.** (2012) PMID:22030098
   Supports diet: Before endurance-style exercise, take in carbohydr...
10. COHORT 2 CITES N=27 **Circulatory response to exercise relative to oxygen uptake assessed in the follow-up of patients with fatty acid beta-oxidation disorders** (2024) PMID:5cbd70ec63c5d3c884996c165eeb875e76a11faa
    Supports exercise: If you ever develop confirmed CPT2-related symptom...
11. CASE REPORT N=1 **Carnitine palmitoyltransferase 2 deficiency: the time-course of blood and urinary acylcarnitine levels during initial L-carnitine supplementation.** (2010) PMID:20543534
    Supports L-carnitine recommendation
12. CASE SERIES N=6 **Long-term follow-up of bezafibrate treatment in patients with the myopathic form of carnitine palmitoyltransferase 2 deficiency.** (2010) PMID:20505667
    Supports Bezafibrate pharmaceutical recommendation
13. REVIEW **Potential of fibrates in the treatment of fatty acid oxidation disorders: revival of classical drugs?** (2006) PMID:16763897
    Supports Bezafibrate pharmaceutical recommendation
14. IN VITRO **Bezafibrate can be a new treatment option for mitochondrial fatty acid oxidation disorders: evaluation by in vitro probe acylcarnitine assay.** (2012) PMID:22841441
    Supports Bezafibrate pharmaceutical recommendation
15. **Identification of novel functional brain proteins for treatment-resistant schizophrenia: Based on a proteome-wide association study.** (2023) PMID:37055858
    PRS correlation: Autophagy (Functional) - A proteome-wide association study (PWAS) identified CPT2 as a statistically significant protein asso

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DUOXA2 — Full Report

1. Variant Information

Gene	DUOXA2

Variant ID	rs201506037
Protein Change	p.Y246X
Genotype	T/C
ClinVar Classification	Pathogenic
Pathogenicity Score	35
Predicted Phenotype	Carrier or possibly affected

2. Associated Diseases

DUOXA2-related congenital hypothyroidism

Low thyroid hormone production because the thyroid's iodine-processing step doesn't run efficiently. In children this can affect growth and brain development unless treated early.

For carriers: Most classic cases are autosomal recessive (two affected copies or combined DUOX-system hits). However, some studies report congenital hypothyroidism in children with a single DUOXA2 variant, so carriers can occasionally be affected—often milder or transient, and sometimes influenced by other factors (genetics/iodine).

3. Variant Mechanism

DUOXA2 is like the "helper/escort" that gets DUOX2 to the right place in thyroid cells so it can make hydrogen peroxide (H_2O_2). Think of H_2O_2 as the spark that lets thyroid peroxidase (TPO) attach iodine to thyroglobulin—key steps in making thyroid hormone. When DUOXA2 doesn't work well, DUOX2 can't generate enough H_2O_2, so iodine "processing" in the thyroid becomes inefficient and thyroid hormone production can drop.

Evidence Summary: Across the reviewed literature, DUOXA2 mutations are repeatedly linked to congenital hypothyroidism (CH) due to thyroid dyshormonogenesis—especially when a person has two affected copies (homozygous) or has DUOXA2 plus another DUOX-system gene affected (compound/oligogenic). However, several reports also describe children with only one DUOXA2 mutation (monoallelic/heterozygous) who still had CH ranging from transient to permanent, suggesting that a single variant can sometimes be clinically relevant—likely depending on other genetic or environmental factors such as iodine intake and other H_2O_2-producing systems. For an adult heterozygous carrier identified incidentally (like T/C here),

most evidence supports autosomal recessive inheritance and many carriers are unaffected, but mild/borderline thyroid dysfunction can occur in some monoallelic carriers in pediatric cohorts.

4. Carrier Phenotype

Being heterozygous (T/C) for a pathogenic DUOXA2 variant usually means you carry one working copy and one non-working (or less-working) copy. For many recessive thyroid dyshormonogenesis genes, carriers are often healthy because one working copy can be enough. That said, the DUOX system has a lot of real-world variability. In pediatric cohorts, some children with only one DUOXA2 mutation still had congenital hypothyroidism—often transient, but sometimes permanent—suggesting that a single DUOXA2 hit can occasionally matter, especially if there are other genetic changes in the DUOX pathway (oligogenic patterns) or environmental factors like iodine status. For an adult carrier without known thyroid disease, the most practical takeaway is: you're unlikely to have severe problems, but it's reasonable to periodically check thyroid function and to be attentive during pregnancy planning (for fetal/newborn thyroid health).

Can be symptomatic: Yes

Symptom frequency: Unclear; evidence suggests uncommon but possible in some monoallelic carriers.

5. Documented Triggers

Low iodine intake / iodine status differences (2011)

Reviews of DUOX2/DUOXA2-related disease highlight iodine intake as a factor that may help explain why some people with DUOX-system variants are mild or even transient while others are permanent. When iodine supply is low, the thyroid has less raw material, so an already 'spark-limited' system (DUOXA2/DUOX2 making H2O2 for TPO) may struggle more.

6. Evidence-Based Recommendations

Lifestyle

COHORT N=20

Diet

REVIEW

Keep a simple record of any thyroid-related symptoms (energy, cold intolerance, constipation, hair/skin changes) and bring it to checkups if you notice a pattern.

Aim for consistent, adequate iodine intake (use iodized salt at home unless your clinician has told you to restrict sodium; include iodine-containing foods you tolerate such as dairy/seafood/eggs).

Exercise

Exercise normally if you feel well, but treat new, persistent fatigue, slow recovery, or feeling unusually cold during workouts as a cue to consider a thyroid lab check.

Supplements

REVIEW

Iodine (supplement) : Only consider an iodine supplement if a clinician confirms low iodine intake/status; avoid high-dose iodine on your own.

Pharmaceuticals

Important: Consult your doctor before starting any medication.

REVIEW 1 CITES

Levothyroxine (L-T4)	(Thyroid hormone replacement)	If thyroid blood tests show hypothyroidism, discuss levothyroxine with your clinician; it's the standard way to replace what the thyroid can't make. If you were treated for CH as a child and stopped, consider periodic follow-up because thyroid function can drift over time in DUOXA2-related disease.	Side effects (moderate): When dosed too high: palpitations, anxiety, tremor, insomnia, heat intolerance, bone loss over time. When dosed appropriately, side effects are uncommon.

Labs to Check

COHORT 38 CITES N=52

TSH and free T4 (FT4) blood tests : These are the most direct way to see if your thyroid hormone production is keeping up. DUOXA2/DUOX variants can present with mild/borderline patterns in some cases, so checking both TSH and FT4 gives a clearer picture than TSH alone. *(Frequency: Not documented in reviewed literature for asymptomatic carriers; a practical approach is baseline once as an adult, then repeat if symptoms arise or during pregnancy planning.)*

CASE SERIES 5 CITES N=3

Thyroid ultrasound if there is neck fullness, goiter, or persistent abnormal labs : Some DUOXA2-related cases present with goiter (thyroid enlargement). Imaging can help clarify thyroid size/structure when labs suggest strain or when the *(Frequency: As needed based on symptoms/labs (not documented as routine for carriers).)*

neck looks/feels enlarged.

Symptoms to Watch

REVIEW | 1 CITES | SOON

Persistent fatigue, brain fog, low mood, or feeling unusually cold	These can be early signs that thyroid hormone output is running low—thyroid hormone is like the body's 'metabolic thermostat.' If the DUOXA2/DUOX2 H2O2 system is less efficient, hormone production can lag.	*Action: If these symptoms last more than a few weeks or are worsening, ask for TSH and free T4 testing.*

CASE SERIES | 5 CITES | N=3 | SOON

Neck fullness or a visible/enlarging lump in the front of the neck (possible goiter)	Goiter can happen when the thyroid is being 'pushed' by high TSH to work harder to compensate for inefficient hormone synthesis, which is described in DUOXA2-related CH cases.	*Action: Arrange a thyroid exam and consider labs (TSH/FT4) and ultrasound.*

Things to Avoid

REVIEW | Avoid

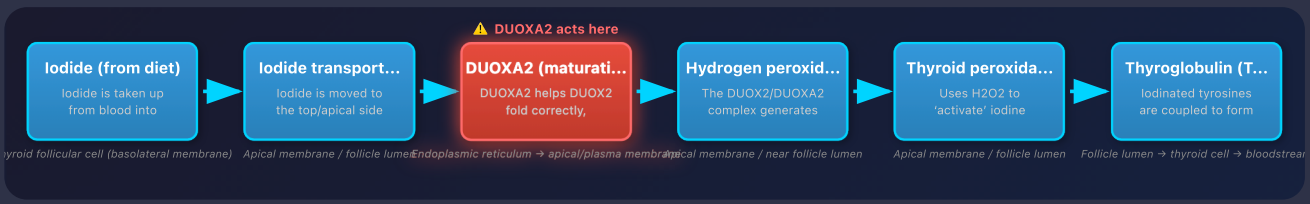
High-dose iodine supplements or 'thyroid support' products with large iodine amounts	(supplement)	In DUOX-system disorders, iodine status is one factor influencing phenotype, but more is not always better. Very high iodine intake can disrupt thyroid function in susceptible people. The reviewed literature supports iodine as a modifier but does not support unsupervised high dosing as a safe strategy for carriers.

7. Key Biological Pathway

🔬 Thyroid hormone synthesis (the DUOX2/DUOXA2 "H2O2 spark" system)

Why this matters: DUOXA2's main job is enabling DUOX2 to generate the hydrogen peroxide that powers thyroid peroxidase (TPO). If that "spark system" underperforms, the thyroid can't efficiently attach iodine to make T4/T3—this is the central reason DUOXA2 variants are linked to congenital hypothyroidism.

Your thyroid makes hormone by taking iodine from your diet and 'building' it onto a protein scaffold. DUOX2 provides the chemical spark (H_2O_2) that lets the building step happen, and DUOXA2 is the helper that makes DUOX2 mature and reach the right spot in the cell to do its job.



When this pathway is impaired:

If DUOXA2 is less functional, DUOX2 can't reliably generate enough H_2O_2. Without enough H_2O_2, TPO can't efficiently attach iodine to thyroglobulin, so thyroid hormone output may be low—leading to hypothyroidism (often congenital) and sometimes goiter as the thyroid tries to compensate.

Other Related Pathways

Thyroid hormone synthesis

KEGG: hsa04918

View Details →

Associated Conditions (KEGG)

- H00251 Thyroid dyshormonogenesis
- 09150 Organismal Systems
- 09152 Endocrine system
- 04918 Thyroid hormone synthesis
- 405753 (DUOXA2)

8. Emergency Protocol

Not documented in reviewed literature for DUOXA2 heterozygous carriers. If you ever develop severe symptoms suggestive of profound hypothyroidism (marked slowing, confusion) or hyperthyroid symptoms from over-replacement (if on levothyroxine), seek urgent medical care.

Warning Signs:

- Rapidly worsening confusion or extreme drowsiness
- Severe shortness of breath or chest pain

- If on thyroid hormone: new palpitations with dizziness/fainting

9. Protein Information

Protein Length	320 amino acids
Function	Required for the maturation and transport of functional DUOX2 from the endoplasmic reticulum to the plasma membrane (PubMed:16651268). Recruits DUOX2 to the apical cell membrane (PubMed:39126279)
Subcellular Location	Endoplasmic reticulum membrane; Apical cell membrane
Known Variants	2

10. Key References

Key References

1. REVIEW 1 CITES **The role of DUOXA2 in the clinical diagnosis of paediatric congenital hypothyroidism** (2024) PMID:fd8da8b4e31c3a429c2e94b219393628daf2d011
   Supports variant mechanism understanding
2. REVIEW **Iodide handling disorders (NIS, TPO, TG, IYD).** (2017) PMID:28648508
   Supports variant mechanism understanding
3. CASE SERIES N=75 **A novel missense mutation (I26M) in DUOXA2 causing congenital goiter hypothyroidism impairs NADPH oxidase activity but not protein expression.** (2015) PMID:25675383
   Supports variant mechanism understanding
4. COHORT N=599 **Large-scale screening and functional study of DUOXA2 variant in 599 Chinese patients with congenital hypothyroidism.** (2025) PMID:40510014
   Supports variant mechanism understanding
5. CASE-CONTROL N=203 **Common and Rare DUOX Variants in Patients With Congenital Hypothyroidism: Case-control Study and Family-based Analysis.** (2025)

PMID:39988947

Supports variant mechanism understanding

6. REVIEW **DUOXS defects: Genotype-phenotype correlations.** (2011) PMID:21511237

   Documents trigger: Low iodine intake / iodine status differences

7. COHORT N=20 **[Characteristics of DUOXA2 gene mutation in children with congenital hypothyroidism].** (2017) PMID:28100324

   Supports carrier phenotype information

8. CASE SERIES 5 CITES N=3 **Persistent goiter with congenital hypothyroidism due to mutation in DUOXA2 gene** (2020) PMID:63fd95470800c9f5c927cc6eeb8a81b0bf57a62d

   Supports carrier phenotype information

9. CASE REPORT N=1 **Fetal Goitrous Hypothyroidism and Polyhydramnios in a Patient with Compound Heterozygous DUOXA2 Mutations.** (2018) PMID:30110704

   Supports lifestyle: If you're planning pregnancy (or are pregnant), pr...

10. REVIEW **Genetic causes of congenital hypothyroidism due to dyshormonogenesis.** (2011) PMID:21543982

    Supports Iodine (supplement) recommendation

11. REVIEW 1 CITES **Diagnostic options, physiopathology, risk factors and genetic causes of permanent congenital hypothyroidism: A narrative review.** (2024) PMID:39359448

    Supports Levothyroxine (L-T4) pharmaceutical recommendation

12. COHORT 38 CITES N=52 **DUOX2/DUOXA2 Mutations Frequently Cause Congenital Hypothyroidism that Evades Detection on Newborn Screening in the United Kingdom** (2019) PMID:f1206fe1a2667efac9d651cb18feaf2e727eda5c

    Supports TSH and free T4 (FT4) blood tests monitoring

Loss-of-Function Gene Variants

Genes where one copy carries a loss-of-function variant. Having one working copy is typically sufficient, but these may contribute to subtle biological differences.

GSTA4 — Full Report

1. Variant Information

Gene	GSTA4
Variant ID	rs749259552
Protein Change	p.S37C
Genotype	CTG/C
ClinVar Classification	Not Applicable
Pathogenicity Score	17
Predicted Phenotype	Likely carrier

2. Associated Diseases

Bladder cancer susceptibility (Tunisian cohort finding)

In one Tunisian case-control study, a heterozygous genotype for a specific GSTA4 SNP (rs17614751, not your variant) was linked with higher odds of bladder cancer, especially in non-smokers in that dataset.

For carriers: This is a human association signal but it involves a different GSTA4 variant than yours, so it cannot be directly applied to rs749259552. Still, it supports the idea that GSTA4 variation can matter for bladder cancer risk in some populations. (Ben Fatma 2022)

Gum inflammation risk biology

Multiple integrative analyses identified GSTA4 among genes linked to periodontitis biology and as a diagnostic biomarker; one study used Mendelian randomization approaches suggesting a causal relationship at the gene level.

For carriers: These are gene-level/statistical links and do not tell us what your specific variant does or what a heterozygous carrier should expect. Useful mainly as a clue that oxidative-stress handling (including GSTA4) is part of gum disease biology. (Mediators Inflamm 2025; BMC Oral Health 2025)

Migraine susceptibility (lower GSTA4 protein)

A genetic study of blood proteins suggested that lower circulating GSTA4 protein levels have a causal effect increasing migraine risk.

For carriers: This suggests that having less GSTA4 activity/expression could matter for migraine biology, but it does not test rs749259552 specifically and does not prove your carrier status changes migraine risk. (Nature Communications 2022)

Atopic dermatitis flare tendency (oxidative stress link)

In a mouse model and patient lesion analyses, lower GSTA4 expression was linked with atopic dermatitis lesions and recurrence; boosting NRF2-driven GSTA4 reduced inflammation and ROS in experiments.

For carriers: This is not a variant study; it's about gene expression regulation. It supports a practical focus on oxidative stress control for skin inflammation, but does not predict symptoms for carriers of rs749259552. (J Invest Dermatol 2025)

Chemotherapy-related hearing loss vulnerability

In female mice, losing Gsta4 made cisplatin-related hearing loss worse, consistent with GSTA4 protecting inner-ear cells by clearing 4-HNE.

For carriers: Applies most strongly to complete loss (knockout) in mice; carrier implications in humans are not documented in reviewed literature. Still, it flags GSTA4 as a potential modifier of cisplatin side effects. (Nature Communications 2019)

3. Variant Mechanism

GSTA4 is one of your body's "cleanup crew" enzymes. When your cells are under oxidative stress (from inflammation, toxins, smoking, alcohol, certain drugs, etc.), fats in cell membranes can get damaged and form a reactive byproduct called 4-HNE. Think of 4-HNE like corrosive smoke produced by a small kitchen fire—if it builds up, it can damage proteins and DNA and amplify inflammation. GSTA4 helps neutralize (detoxify) 4-HNE by attaching it to glutathione so it can be safely cleared. Your specific variant (rs749259552) has an unknown protein change and is not functionally characterized in the papers provided, so we cannot say it definitely reduces or increases enzyme activity. Not documented in reviewed literature.

Evidence Summary: Across multiple studies, GSTA4 repeatedly shows up as a key "buffer" against oxidative stress and lipid-peroxidation damage (4-HNE). Animal and cell studies show that losing Gsta4 can increase sensitivity to oxidative injury and inflammation in some tissues (e.g., cells exposed to oxidants; liver under chronic alcohol exposure; cisplatin ototoxicity), while in at least one heart model the body can compensate by revving up the NRF2 antioxidant program (an adaptive 'backup system'). In human genetic studies, changes related to GSTA4 have been linked to disease risk or outcomes (e.g., bladder cancer risk for a different GSTA4 SNP; migraine risk associated with lower blood GSTA4 protein; periodontitis biomarker/causal-gene analyses), but none of the provided papers specifically evaluate rs749259552. So for you as a heterozygous carrier, the most defensible, practical takeaway is: you may want to be proactive about managing oxidative stress and inflammation exposures, because GSTA4 sits in that detox pathway—yet we cannot quantify your personal risk from this variant based on the reviewed literature.

4. Carrier Phenotype

You're heterozygous (a 'carrier') for rs749259552 in GSTA4, meaning you have one copy of this variant and one typical copy. For many detox/antioxidant genes, carriers often feel completely normal in day-to-day life because one working copy can be enough. In the literature you provided, there are no studies that evaluate rs749259552 specifically, and there are no reports describing symptoms in heterozygous carriers of this variant. So the honest bottom line

is: we can't say you will have symptoms because of this variant. What we *can* do is use what GSTA4 does biologically to guide practical habits—especially around oxidative stress and inflammation—because that's the theme across the studies.

Can be symptomatic: Unknown/Rarely

Symptom frequency: Not documented in reviewed literature

5. Documented Triggers

Cisplatin chemotherapy exposure (2019)

Cisplatin increases oxidative stress and lipid peroxidation; when Gsta4 is absent in mice, 4-HNE builds up in the inner ear and hearing loss is worse (especially in female mice). In kidney models, cisplatin triggers ferroptosis/lipid peroxide accumulation and Gsta4 is among regulated genes in protective responses. The practical takeaway is that if you ever need cisplatin, it's worth proactively discussing hearing and kidney monitoring and oxidative-stress mitigation with your oncology team—because GSTA4 is part of the defense system in these models.

Chronic alcohol intake and especially binge drinking on top of chronic intake (2018)

In male mice lacking Gsta4, chronic ethanol feeding plus an ethanol binge caused more liver inflammation, broader distribution of 4-HNE-adducted proteins, and higher inflammatory markers compared with wild-type. This suggests that when the 4-HNE 'cleanup' pathway is impaired, alcohol-related oxidative stress hits harder—especially with binge patterns that spike oxidative damage.

High oxidative-stress exposures (oxidants/chemicals, heat, radiation) (2013)

Cell and mechanistic work emphasizes that oxidants and electrophiles increase 4-HNE; in Gsta4-null cells, oxidant-induced toxicity is stronger and linked to more 4-HNE adducts and DNA damage. Real-world analogs include heavy chemical exposures or any situation that meaningfully increases oxidative stress burden.

Iron overload / high iron-driven oxidative stress (2002)

In mice, iron overload increases free radical production and induces GSTA4 in liver and kidney, consistent with GSTA4 being part of the adaptive response when oxidative stress is high. This doesn't prove that 'iron is bad' for carriers, but it flags iron-overload states as oxidative-stress conditions where GSTA4 is relevant.

Skin exposure to strong chemical tumor promoters (TPA model) (2010)

In mouse skin carcinogenesis experiments, Gsta4 influenced susceptibility to tumor promotion after TPA exposure, consistent with a role in managing oxidative/lipid-peroxidation stress in skin.

Tobacco exposure intensity (for bladder cancer risk modeling) (2022)

In the bladder cancer decision-tree analysis, heavy tobacco exposure (>20 pack-years) was a major classifying risk factor. This isn't specific to your variant, but it's an important environmental oxidative/toxin exposure that interacts with genetic risk in that cohort.

6. Evidence-Based Recommendations

Lifestyle

CASE-CONTROL N=504

Treat smoking (including secondhand smoke) as a high-priority 'avoid' and get support to quit if it applies.

ANIMAL 13 CITES

Be especially cautious with alcohol patterns—if you drink, aim to avoid binge drinking and keep intake modest.

Take gum health seriously: floss/clean between teeth most days and keep regular dental cleanings.

ANIMAL

If you have a condition that could cause iron overload, don't self-supplement iron unless you've checked levels with your clinician.

Diet

Build meals around glutathione 'raw materials': include a protein source plus sulfur-rich foods most days (eggs, fish/meat/legumes; and garlic/onion/crucifers like broccoli).

ANIMAL 13 CITES

If you drink alcohol, eat with it and hydrate—avoid drinking on an empty stomach, and avoid 'catch-up' weekend binges.

Exercise

Aim for consistent, moderate exercise (like brisk walking, cycling, swimming) most weeks, and ramp up gradually rather than doing sudden 'all-out' sessions after time off.

Supplements

IN VITRO

L-glutamine: Not a routine 'must,' but if you're considering it for gut health or recovery, discuss with your clinician—there is lab evidence it can improve glutathione-related redox balance during 4-HNE stress. *(Dosage: Not specified in reviewed literature for humans (cell study used 0.25 mmol/L).)*

ANIMAL

Vitamin E: Avoid high-dose self-prescribing, but ensure you're not deficient; in a mouse hepatocyte model, vitamin E prevented iron-induced toxicity and the associated GSTA4 induction (a sign it reduced oxidative stress load). *(Dosage: Not specified in reviewed literature.)*

Pharmaceuticals

Important: Consult your doctor before starting any medication.

ANIMAL 44 CITES

Cisplatin (context: if prescribed) (Platinum chemotherapy)

If cisplatin is ever part of your cancer care, proactively ask your oncology team about hearing monitoring (baseline and follow-up audiology), kidney monitoring, and side-effect prevention strategies. This is not because your rs749259552 carrier status is proven to increase risk, but because GSTA4 is protective in cisplatin-toxicity models, and it's reasonable to be extra attentive to these organs.

Side effects (significant): Cisplatin can cause permanent hearing loss and acute kidney injury among other side effects.

Labs to Check

Dental periodontal evaluation (gum pocketing/bleeding assessment): Because GSTA4 is repeatedly implicated as a biomarker/causal gene in periodontitis multiomics work, staying ahead of gum inflammation is a practical way to reduce chronic oxidative stress burden. *(Frequency: At routine dental visits; consider earlier review if you notice bleeding gums or persistent bad breath.)*

ANIMAL 44 CITES

If ever treated with cisplatin: audiology (hearing test) and kidney labs (creatinine/BUN): In animal models, Gsta4 protects against cisplatin ototoxicity and is involved in protective transcriptional responses in cisplatin kidney injury. Monitoring helps catch toxicity early. *(Frequency: Baseline before cisplatin and at intervals set by oncology; urgent testing if new tinnitus/hearing changes or reduced urine output.)*

ANIMAL

Iron status (ferritin, transferrin saturation) if you have a reason to suspect iron overload or are considering iron supplements: Iron overload drives oxidative stress and induces GSTA4 in mouse liver/kidney; knowing your iron status helps avoid unnecessary oxidative burden from excess iron. *(Frequency: As clinically indicated (not routine for everyone).)*

Symptoms to Watch

ANIMAL | 44 CITES | URGENT

New ringing in the ears (tinnitus), muffled hearing, or trouble understanding speech—especially during chemotherapy

In cisplatin models, lack of Gsta4 worsens inner-ear damage due to 4-HNE buildup. While your variant's effect isn't known, early hearing changes during cisplatin are a red-flag symptom worth rapid attention.

Action: Tell your oncology team promptly and request audiology evaluation; do not wait for the next scheduled visit.

ANIMAL | URGENT

Reduced urine output, swelling, or sudden fatigue during chemotherapy

Cisplatin can trigger acute kidney injury driven by oxidative stress/ferroptosis pathways where Gsta4 is a regulated gene in protective responses.

Action: Seek same-day medical advice; kidney labs may be needed quickly.

SOON

Bleeding gums when brushing/flossing, persistent gum swelling, or loosening teeth

Periodontitis is an inflammatory/oxidative-stress condition and GSTA4 is highlighted as a biomarker/causal gene in multiomics analyses; ongoing gum inflammation can become a chronic source of oxidative stress.

Action: Schedule a dental evaluation; ask about periodontal measurements and a tailored home-care plan.

Things to Avoid

ANIMAL | 13 CITES | Avoid

Binge drinking (large alcohol intake in a short time), especially on top of regular drinking (lifestyle)

In Gsta4 knockout mice, an ethanol binge on top of chronic intake markedly increased liver injury and inflammation, consistent with 4-HNE detox pathways being overwhelmed when Gsta4 is missing.

CASE-CONTROL | N=504 | Strictly Avoid

Smoking and heavy tobacco exposure (lifestyle)

Tobacco use intensity was a major risk factor class in the bladder cancer risk model, and smoking increases oxidative stress and toxic exposures that generate lipid peroxidation products like 4-HNE—directly increasing demand on GSTA4-related detox.

ANIMAL | Avoid

Unnecessary iron supplementation (supplement)

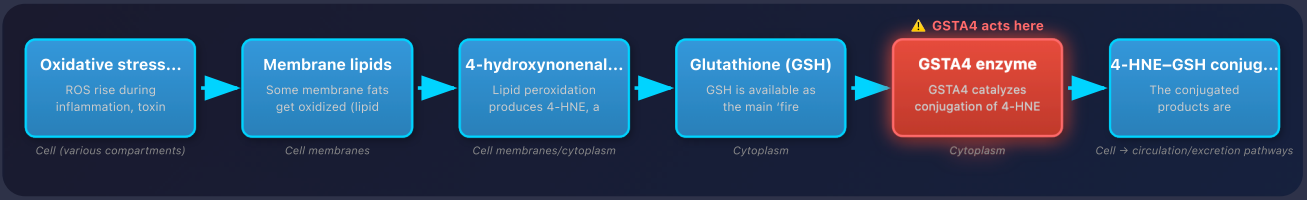
Iron overload increases oxidative stress and triggers GSTA4 induction in mouse liver/kidney; extra iron when not needed can increase oxidative burden.

7. Key Biological Pathway

Glutathione detoxification of lipid peroxidation (4-HNE clearance)

Why this matters: This is the core reason GSTA4 matters: it helps mop up 4-HNE, a toxic byproduct that rises during oxidative stress and can drive inflammation and tissue injury. Many of the reviewed papers—across skin, liver, kidney injury models, and chemotherapy toxicity—tie GSTA4's protective role directly to controlling 4-HNE and downstream oxidative damage.

When your cells experience "rust-like" stress (oxidative stress), damaged fats create a reactive chemical called 4-HNE. GSTA4 helps attach 4-HNE to glutathione—your body's main antioxidant—so it becomes less harmful and can be cleared. If this cleanup step is weaker, 4-HNE can build up and irritate tissues, fueling inflammation and damage.



When this pathway is impaired:

If GSTA4 activity or expression is reduced, 4-HNE can accumulate, stick to proteins/DNA ('adducts'), and amplify inflammatory signaling and cell stress. In models lacking Gsta4, this shows up as higher oxidative damage and inflammation under stressors like oxidants, ethanol, or cisplatin—though some tissues can partially compensate by turning on NRF2 antioxidant genes (a backup response). (Park 2019; Kono 2018; Zhang 2013; Zhang 2013; Pan 2025)

Other Related Pathways

Glutathione metabolism
KEGG: hsa00480
View Details →

Metabolism of xenobiotics by cytochrome P450
KEGG: hsa00980
View Details →

Drug metabolism - cytochrome P450
KEGG: hsa00982
View Details →

Drug metabolism - other enzymes
KEGG: hsa00983
View Details →

Metabolic pathways
KEGG: hsa01100
View Details →

Platinum drug resistance
KEGG: hsa01524
View Details →

Pathways in cancer
KEGG: hsa05200
View Details →

Chemical carcinogenesis - DNA adducts
KEGG: hsa05204
View Details →

Chemical carcinogenesis - receptor activation

KEGG: hsa05207

View Details →

Chemical carcinogenesis - reactive oxygen species

KEGG: hsa05208

View Details →

Hepatocellular carcinoma

KEGG: hsa05225

View Details →

Fluid shear stress and atherosclerosis

KEGG: hsa05418

View Details →

8. Emergency Protocol

No illness-specific emergency protocol is described for GSTA4 variants in the reviewed literature. In general, if you're acutely ill and unable to eat/drink, or you have severe symptoms (confusion, chest pain, trouble breathing), seek urgent medical care. If you are receiving cisplatin and develop new hearing changes or signs of kidney problems, treat that as urgent and contact your oncology team immediately (cisplatin toxicity models implicate GSTA4 in protection).

Warning Signs:

- New tinnitus or sudden hearing change during cisplatin
- Marked drop in urine output, swelling, or severe fatigue during cisplatin

9. Protein Information

Protein Length	222 amino acids
Function	GSTA4 is an important gene that helps protect our cells by detoxifying harmful substances. When loss-of-function variants occur in this gene, the enzyme it produces becomes less effective at cleaning
Subcellular Location	Location not specified

Known Variants	0

10. Key References

Key References

1. ANIMAL 44 CITES **GSTA4 mediates reduction of cisplatin ototoxicity in female mice** (2019) PMID:31515474
   Supports variant mechanism understanding
2. ANIMAL 13 CITES **Knockout of the Gsta4 Gene in Male Mice Leads to an Altered Pattern of Hepatic Protein Carbonylation and Enhanced Inflammation Following Chronic Consumption of an Ethanol Diet** (2018) PMID:ca0531351b9d446ee138aaec55da562d81223c6c
   Supports variant mechanism understanding
3. ANIMAL **Protection from oxidative and electrophilic stress in the Gsta4-null mouse heart.** (2013) PMID:23690225
   Supports variant mechanism understanding
4. IN VITRO 35 CITES **Gsta4 Null Mouse Embryonic Fibroblasts Exhibit Enhanced Sensitivity to Oxidants: Role of 4-Hydroxynonenal in Oxidant Toxicity.** (2013) PMID:01c2cb473879bdcbc5ad7027f221930dc9ba3877
   Supports variant mechanism understanding
5. **Genetic analyses identify pleiotropy and causality for blood proteins and highlight Wnt/β-catenin signalling in migraine.** (2022) PMID:35546551
   Supports variant mechanism understanding
6. ANIMAL **Differential effects of iron overload on GST isoform expression in mouse liver and kidney and correlation between GSTA4 induction and overproduction of free radicles.** (2002) PMID:11755321
   Documents trigger: Iron overload / high iron-driven oxidative stress
7. ANIMAL **Evidence that Gsta4 modifies susceptibility to skin tumor development in mice and humans.** (2010) PMID:20966433
   Documents trigger: Skin exposure to strong chemical tumor promoters (TPA model)
8. CASE-CONTROL N=504 **Development of a custom next-generation sequencing panel for the determination of bladder cancer risk in a Tunisian cohort.** (2022) PMID:34854013
   Documents trigger: Tobacco exposure intensity (for bladder cancer risk modeling)

9. **Causal Gene Identification and Biomarker Prioritization in Periodontitis via Integrative Multiomics and Mendelian Randomization.** (2025) PMID:41333919
   Supports lifestyle: Take gum health seriously: floss/clean between tee...
10. IN VITRO **l-Glutamine Attenuates Apoptosis in Porcine Enterocytes by Regulating Glutathione-Related Redox Homeostasis.** (2018) PMID:29659951
    Supports L-glutamine recommendation
11. ANIMAL **Farnesoid X receptor protects against cisplatin-induced acute kidney injury by regulating the transcription of ferroptosis-related genes.** (2022) PMID:35767918
    Supports Cisplatin (context: if prescribed) pharmaceutical recommendation
12. **Integrative bioinformatics analysis identifies glutathione metabolism-related genes as diagnostic biomarkers for periodontitis.** (2025) PMID:41053677
    Supports Dental periodontal evaluation (gum pocketing/bleeding assessment) monitoring
13. ANIMAL **Retracing from Outcomes to Causes: NRF2-Driven GSTA4 Transcriptional Regulation Controls Chronic Inflammation and Oxidative Stress in Atopic Dermatitis Recurrence.** (2025) PMID:38879155
    NRF2-driven upregulation of GSTA4 reduces ROS and inflammatory responses; decreased GSTA4 was seen in AD lesions and linked to recurrence biology.
14. **Glutathione** (2018) PMID:29681884
    PRS correlation: Arachidonic Acid - PMID 29681884 reviews glutathione-dependent detoxification of lipid peroxidation products in neurode

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PCSK4 — Full Report

1. Variant Information

Gene	PCSK4
Variant ID	rs200944148
Protein Change	p.T6G
Genotype	G/A
ClinVar Classification	Not Applicable
Pathogenicity Score	16

Predicted Phenotype	Likely carrier

2. Associated Diseases

Sperm function–related fertility issues

Sperm can look normal but have trouble completing the final steps needed to fertilize an egg—especially the timing of capacitation, the acrosome reaction, and binding to the egg's outer layer.

For carriers: Clear effects are shown when PCSK4 is fully absent in mice (both copies). Symptoms in heterozygous human carriers are not documented in reviewed literature; if fertility concerns arise, this biology supports focusing on functional sperm testing rather than assuming a problem.

Possible ovarian support role (emerging)

In female mice lacking PCSK4, fertility can be reduced, possibly due to changes in how ovarian follicles mature.

For carriers: Evidence is from animal models and does not establish risk for heterozygous human carriers (not documented in reviewed literature).

Tumor-related hypoglycemia (big IGF2)

Some large tumors produce an oversized form of IGF2 ('big IGF2') that can drive dangerously low blood sugar; lower PCSK4 relative to IGF2 in the tumor may contribute to this imbalance.

For carriers: This is about PCSK4 expression inside tumors, not inherited carrier status. No evidence in reviewed literature that rs200944148 carriers have increased NICTH risk.

Endometrial cancer prognosis markers (expression-based)

PCSK4 expression can be part of multi-gene panels that correlate with overall survival and immune features of endometrial tumors.

For carriers: These studies use tumor gene expression, not germline rs200944148 genotype. Carrier implications are not documented in reviewed literature.

Chromosomal duplication-linked infertility risk

A specific DNA duplication on chromosome 19p13.3 was seen in a subset of infertile men with severe testicular findings; PCSK4 was within a broader duplicated region/gene network in some cases.

For carriers: This is a large duplication (copy-number change), not the rs200944148 single-variant carrier state. It does not establish risk for rs200944148 heterozygous carriers (not documented in reviewed literature).

3. Variant Mechanism

PCSK4 makes an enzyme (a protein-cutting 'molecular scissors') that helps activate other proteins by trimming them into their working form. Think of PCSK4 as a quality-control worker

in reproductive cells: it snips certain “pre-proteins” on sperm (and to a lesser extent in ovary/placenta) so they can do their jobs during the steps that let sperm fertilize an egg. Your result (rs200944148, G/A, heterozygous) means you carry one typical copy and one altered copy of PCSK4. The papers provided do not study this specific variant, and they do not show that carriers of single PCSK4 variants reliably have symptoms. So we cannot assume it changes enzyme function or fertility. What the literature *does* show is that when PCSK4 function is fully absent (in mice), sperm have trouble with key fertilization steps like capacitation timing, acrosome reaction control, and binding to the egg’s outer layer. That’s the biology to keep in mind if fertility questions ever come up.

Evidence Summary: Most of what we know about PCSK4 comes from mouse “knockout” studies where both copies are disrupted. In those animals, sperm can look normal but fertilize poorly, showing that PCSK4 matters for sperm function rather than sperm production (1997, 2006, 2012, 2010). A human study shows PCSK4 sits on the sperm head/acrosome region and that antibodies against it can interfere with sperm’s ability to penetrate an egg in experimental systems (2019). Separately, some cancer gene-expression papers include PCSK4 as part of prognostic signatures in uterine endometrial cancer, but they do not link the *rs200944148* genotype to risk or outcomes (2018, 2021). Bottom line for a heterozygous carrier: based on the reviewed literature, clear health effects are *not documented*. If there is any relevance, it would most plausibly relate to reproductive biology—especially male factor fertility—because that is where PCSK4’s role is best supported (mouse and sperm-function studies).

4. Carrier Phenotype

You’re a heterozygous carrier (one copy G, one copy A) of rs200944148 in PCSK4. Based on the papers provided, there isn’t evidence that single-copy carriers have a consistent medical syndrome. If PCSK4 variants matter clinically, the most biologically plausible area is fertility—especially sperm function—because PCSK4 is mainly active in sperm and testicular germ cells. But the strongest evidence of fertility problems comes from animals missing *both* copies of PCSK4 or from experiments that directly block the enzyme in sperm. That’s very different from carrying one copy of a variant with unknown protein impact. Practical meaning: if you (or your family) ever face unexplained fertility challenges, it would be reasonable to mention this PCSK4 finding to a fertility specialist, not because it proves a cause, but because it points toward looking carefully at sperm function tests (capacitation/acrosome-related measures) rather than assuming hormone or sperm-count issues.

Can be symptomatic: Unknown/Rarely

Symptom frequency: Not documented in reviewed literature

5. Documented Triggers

Blocking or inhibiting PCSK4 activity in sperm (experimental peptide inhibitor) (2011)

In mouse sperm experiments, a peptide designed from the PCSK4 prodomain (proPC4(75–90)) strongly inhibited PCSK4 activity and reduced fertilization in a dose-dependent way, especially by lowering capacitation and zona pellucida–induced acrosome reaction. This is a 'trigger' only in the sense of an experimental way to temporarily mimic low PCSK4 activity.

Anti-PCSK4 antibodies binding sperm (experimental immunocontraception approach) (2019)

In a study developing antibodies against human sperm PCSK4, the antibodies bound the sperm head and interfered with sperm's ability to penetrate the oocyte in experimental systems. This supports that reducing PCSK4 function can impair fertilization.

6. Evidence-Based Recommendations

Lifestyle

REVIEW ANIMAL

If fertility is a current goal, prioritize early evaluation rather than waiting a long time 'just to see.'

ANIMAL

When doing fertility workups, ask whether sperm function testing is appropriate (not just count and motility).

Diet

No special diet is required based on the reviewed PCSK4 literature.

Exercise

No PCSK4-specific exercise restrictions are documented; choose activity based on your overall health and goals.

Supplements

ANIMAL

None specific to PCSK4 : No supplements are supported by the reviewed literature specifically for PCSK4 rs200944148 carriers.

Pharmaceuticals

None found during research

Labs to Check

ANIMAL

If male fertility is a concern: semen analysis plus consideration of functional assays (e.g., capacitation/acrosome reaction testing where available)	: PCSK4 deficiency in mice primarily affects sperm function during capacitation and acrosome reaction rather than causing obvious sperm production defects. If a clinician suspects a functional issue, these tests may be more aligned with PCSK4 biology.	*(Frequency: As clinically indicated during fertility evaluation; frequency not documented in reviewed literature)*

Symptoms to Watch

REVIEW ANIMAL ROUTINE

Difficulty conceiving after 6–12 months of well-timed unprotected intercourse (or sooner if age/known factors apply)	PCSK4 is most strongly tied to sperm's ability to fertilize in animal and sperm-function studies. If conception is taking longer than expected, it's a practical signal to look deeper, even if routine health looks fine.	*Action: Consider a fertility consultation; if male factor is being evaluated, mention the PCSK4 finding and ask whether sperm function testing is appropriate.*

Things to Avoid

ANIMAL Caution

Experimental or off-label agents aimed at inhibiting proprotein convertases for non-medical reasons (especially any that could affect PCSK4)	(pharmaceutical)	PCSK4 activity is important for sperm function in animal and sperm inhibition studies. Intentionally suppressing it could, in theory, impair fertility. Specific real-world drugs that do this are not detailed in the reviewed literature.

7. Key Biological Pathway

Sperm capacitation → acrosome reaction → egg binding (PCSK4-dependent protein activation)

Why this matters: Across the papers, PCSK4's clearest, repeated role is in the chain of events that turns ejaculated sperm into sperm that can bind and penetrate the egg. The knockout and inhibitor studies show that when PCSK4 activity is missing or blocked, the timing and processing of key sperm proteins goes off—leading to reduced fertilization even when sperm production looks normal.

Before sperm can fertilize an egg, they have to "warm up" (capacitation), then release enzymes from the acrosome (acrosome reaction), and finally bind to and penetrate the egg's outer coat (zona pellucida). PCSK4 helps activate and remodel certain sperm surface proteins during this sequence—like flipping the right switches at the right time.

When this pathway is impaired:

When PCSK4 activity is absent (shown in PCSK4-null mice) or chemically blocked (sperm treated with a PCSK4 prodomain-based inhibitor), sperm can capacitate too fast or in an uncoordinated way, undergo acrosome reaction too easily, bind the zona pellucida less well, and fertilize less effectively; embryos produced may also fail to progress normally in some mouse experiments. For a heterozygous human carrier, whether a single-allele variant causes any measurable change is not documented in the reviewed literature.

Other Related Pathways

No metabolic pathways associated with PCSK4 in KEGG. This gene may be involved in protein complexes or signaling rather than metabolic pathways.

8. Emergency Protocol

No PCSK4-specific emergency/illness protocol is documented in reviewed literature. PCSK4-related findings in these papers are mainly reproductive and do not describe acute metabolic crises or emergency triggers.

Warning Signs:

No warning signs documented.

9. Protein Information

Protein Length	318 amino acids
Function	PCSK4 is a gene that produces an enzyme important for turning inactive protein precursors into active molecules, a process essential for normal reproductive functions in both men and women. When the g
Subcellular Location	Location not specified
Known Variants	0

10. Key References

Key References

1. REVIEW ANIMAL **Proprotein convertase subtilisin/kexin type 4 in mammalian fertility: a review.** (2009) PMID:19109312
   Supports variant mechanism understanding
2. ANIMAL **Impaired fertility in mice deficient for the testicular germ-cell protease PC4.** (1997) PMID:9192653
   Supports variant mechanism understanding
3. ANIMAL **Sperm from mice genetically deficient for the PCSK4 proteinase exhibit accelerated capacitation, precocious acrosome reaction, reduced binding to egg zona pellucida, and impaired fertilizing ability.** (2006) PMID:16371590
   Supports variant mechanism understanding
4. ANIMAL **Alteration in the processing of the ACRBP/sp32 protein and sperm head/acrosome malformations in proprotein convertase 4 (PCSK4) null mice.** (2012) PMID:22357636
   Supports variant mechanism understanding

5. ANIMAL **Enzymatic activity of sperm proprotein convertase is important for mammalian fertilization.** (2011) PMID:21302280
   Supports variant mechanism understanding
6. IN VITRO **Human spermatozoa anti-proprotein convertase subtilisin/kexin type 4 synthesis using New Zealand rabbit for novel immunocontraception in males.** (2019) PMID:31294140
   Supports variant mechanism understanding

ITIH2 — Full Report

1. Variant Information

Gene	ITIH2
Variant ID	rs151229507
Protein Change	p.T1H
Genotype	G/C
ClinVar Classification	Not Applicable
Pathogenicity Score	16
Predicted Phenotype	Likely carrier

2. Associated Diseases

Severe viral inflammation risk markers (COVID-19 context)

During severe COVID-19, ITIH2 levels in blood were one of several proteins that differed between survivors and non-survivors and/or tracked with severity in proteomics studies.

For carriers: These studies do not test rs151229507 carriers specifically, and they identify ITIH2 as a *biomarker*, not a genetic cause. Useful as context that ITIH2 participates in inflammatory responses, but it does not mean you're destined for severe COVID-19.

Sepsis-related tissue swelling/inflammation markers

In septic shock, several hyaluronan-related proteins shifted, including lower ITIH2, consistent with major extracellular-matrix and vascular barrier disruption.

For carriers: Not linked to this variant; reflects how ITIH2 behaves during extreme inflammation rather than indicating carrier symptoms.

Lupus activity (kidney involvement) markers

Urine ITIH2 levels were associated with lupus disease activity and correlated with kidney damage measures in an exploratory study.

For carriers: Not evidence that carriers develop lupus. It means ITIH2 can reflect kidney inflammation when lupus is present.

Pregnancy blood-pressure complication markers

ITIH2 abundance in maternal plasma was perturbed in late-onset preeclampsia compared with normotensive pregnancy controls.

For carriers: Not variant-based risk; the study measures protein changes during disease. Pregnancy planning should follow standard obstetric guidance unless other risk factors exist.

Pancreatic cancer blood test research signature

ITIH2 RNA was part of an 8-RNA extracellular-vesicle signature that distinguished pancreatic cancer from controls with high accuracy.

For carriers: This is a diagnostic biomarker research tool, not a statement about genetic risk from rs151229507.

3. Variant Mechanism

ITIH2 makes one of the “heavy chain” building blocks of the inter-alpha-trypsin inhibitor family—proteins that help organize and stabilize the extracellular matrix (the supportive gel-and-fiber “scaffolding” between cells). A key job of ITIH family proteins is to bind to hyaluronan (HA), a sugar-like molecule that forms a slippery, water-holding mesh in tissues. Think of hyaluronan as the body’s ‘gel cushion’ and ITIH2 as a ‘reinforcing strap’ that helps keep that gel structured and well-behaved during inflammation and tissue repair. Your specific variant (rs151229507) is listed as a DNA change in ITIH2, but the papers provided do not describe the exact amino-acid change or prove that this particular G/C genotype alters ITIH2 function or levels. So we can’t say it is harmful or protective based on these papers alone. What we *can* say from the literature is that ITIH2 levels (protein or RNA) often shift during strong inflammatory states (like severe COVID-19, sepsis, lupus activity, preeclampsia) and across several cancers, suggesting ITIH2 sits in a ‘tissue remodeling + inflammation’ control system. If a genetic variant were to modestly change ITIH2 expression or activity, the most plausible downstream effect would be subtle differences in how someone’s tissues handle inflammation and remodeling—not a classic single-gene disorder.

Evidence Summary: Across many proteomics and expression studies, ITIH2 shows up as a marker of disease state/severity rather than a proven cause. In severe COVID-19, higher ITIH2 abundance was seen in survivors compared with non-survivors in one cohort (suggesting ITIH2 may track with a more favorable response) and ITIH2 was also proposed as an early severity predictor in another study; the direction of change depends on cohort/analysis, which is common for 'response' proteins. In septic shock, ITIH2 levels were decreased compared with controls. In lupus, urine ITIH2 tracked with disease activity and kidney involvement. In several cancers, ITIH2 is proposed as a diagnostic/prognostic biomarker or is downregulated in tumors, while in a lung cancer microenvironment study ITIH2 helped build a hyaluronan-rich matrix that supported invasion. These mixed patterns fit with ITIH2 being part of the body's extracellular-matrix remodeling response, which can be beneficial in healing but can be 'hijacked' in cancer. For a *heterozygous carrier* of rs151229507: none of the provided papers report a carrier syndrome, penetrant disease, or specific symptoms tied to having one copy of this variant. The most responsible interpretation from this literature is: this variant is currently best viewed as an uncertain marker, and your day-to-day health planning should focus on general inflammation-resilience and appropriate, guideline-based screening—rather than assuming you have an ITIH2-driven disease.

4. Carrier Phenotype

With one copy of rs151229507 (G/C), you are a heterozygous carrier. Based on the papers reviewed, there is no documented 'ITIH2 carrier condition' and no evidence that carriers routinely develop a predictable set of symptoms. What *is* consistent across studies is that ITIH2 levels move up or down when the body is under major inflammatory or tissue-remodeling stress (severe infection, autoimmune flares, certain pregnancy complications, and cancers). So the practical takeaway is not "you will get X," but "this gene sits in an inflammation-and-tissue-scaffolding system, so it's sensible to be proactive about reducing inflammation load and responding early to serious illness."

Can be symptomatic: Unknown/Rarely

Symptom frequency: Unknown

5. Documented Triggers

Severe viral infection causing respiratory failure (severe COVID-19) (2021)

In severe COVID-19 cohorts, ITIH2 abundance differed between survivors and non-survivors and/or tracked with severity, consistent with ITIH2 being part of the body's acute inflammation + tissue remodeling

response. A ‘trigger’ here is the high inflammatory load from severe infection—this is when the HA/ECM system gets heavily remodeled.

Sepsis / septic shock (overwhelming infection-driven inflammation) (2025)

In septic shock patients, hyaluronan-related proteins including ITIH2 were decreased compared to controls, aligning with major endothelial/ECM disruption. The trigger is the extreme systemic inflammation and vascular leak that forces the HA matrix to remodel rapidly.

Active lupus inflammation (especially kidney involvement) (2022)

Urine ITIH2 was associated with lupus disease activity and correlated with renal damage, suggesting that during autoimmune kidney inflammation, ITIH2-related pathways are ‘turned up/down’ and measurable.

Pregnancy complicated by preeclampsia (late-onset) (2022)

Maternal plasma ITIH2 was perturbed in late-onset preeclampsia versus controls, consistent with pregnancy vascular/inflammatory remodeling affecting HA/ECM-associated proteins.

Tumor microenvironment EMT program (ZEB1-high state) (2025)

In a lung cancer model, ZEB1 upregulated ITIH2 along with HAS2; ITIH2 supported HA matrix formation and increased migration/invasion. The trigger is the EMT switch within tumors, often influenced by stromal interactions.

Depot medroxyprogesterone acetate (DMPA) contraceptive exposure (cervical tissue context) (2022)

DMPA use was associated with altered protein levels of ITIH2 in cervicovaginal lavage in a multi-omics study of epithelial integrity and immune activation. The trigger is a hormone-driven change in mucosal barrier and immune signaling where HA/ECM-associated proteins can shift.

6. Evidence-Based Recommendations

Lifestyle

COHORT N=33

Treat serious infections as a ‘higher stakes’ situation: don’t tough it out—seek care early if you have high fever, shortness of breath, confusion, or rapidly worsening symptoms.

COHORT N=96

Diet

None found during research

If you use (or are considering) DMPA contraception, consider discussing mucosal/barrier health with your clinician (e.g., recurrent irritation, infections, or concerns about STI risk).

Exercise

None found during research

Supplements

None found during research

Pharmaceuticals

Important: Consult your doctor before starting any medication.

ANIMAL

Sincalide (as an ITIH2 inhibitor in cancer models)	(Cholecystokinin analog (repurposing candidate in research))	Not a medication to use for prevention or self-treatment. It was identified as an ITIH2-pathway inhibitor in a lung cancer metastasis model; if you ever face a cancer diagnosis, you could mention this paper to your oncology team as an example of the HA/ITIH2 network being druggable in research.	Side effects (moderate): Not documented in reviewed literature for this specific use case; sincalide has clinical uses for gallbladder testing, but side effects in oncology contexts were not provided in the abstract.

Labs to Check

CASE-CONTROL N=501

Age- and sex-appropriate cancer screening (standard-of-care, individualized)	: ITIH2 is repeatedly identified as a cancer biomarker (prostate urine proteome; pancreatic EV RNA signature; HCC EV proteomics) and is often downregulated in tumor tissues. This does not prove your variant causes cancer, but it supports the practical value of staying up to date with routine screening so cancers are caught early, when tissue remodeling is less advanced.	*(Frequency: Follow standard guidelines for your age/sex/family history (not specified in reviewed literature).)*

CASE-CONTROL

: Urine ITIH2 tracked with lupus activity and kidney involvement in one study, which

If you have symptoms suggestive of autoimmune disease or kidney inflammation, ask about urine testing (urinalysis/protein) as part of evaluation.	highlights that kidney inflammation can be reflected in urine proteins. The practical lesson is to take persistent swelling, foamy urine, blood in urine, or unexplained high blood pressure seriously.	*(Frequency: Symptom-triggered; routine frequency not documented in reviewed literature.)*

Symptoms to Watch

COHORT N=33 URGENT

Shortness of breath, chest tightness, or oxygen levels dropping during a respiratory infection	Severe COVID-19 studies show ITIH2 is part of a blood protein panel that differentiates outcomes/severity, consistent with ITIH2 being involved when inflammation becomes systemic and tissue barriers are stressed.	*Action: Seek urgent medical evaluation, especially if symptoms worsen over hours to a day or you have risk factors (age, chronic disease).*

CASE SERIES N=29 EMERGENCY

Signs of severe systemic infection: high fever with confusion, very low blood pressure symptoms (fainting), rapid breathing, or severe weakness	In septic shock, ITIH2 and other hyaluronan-associated proteins are altered, reflecting major vascular/ECM dysfunction. These are emergencies regardless of genotype, but this pathway evidence reinforces taking them seriously.	*Action: Call emergency services or go to the ER immediately.*

CASE-CONTROL SOON

Things to Avoid

COHORT N=33 Avoid

Ignoring or delaying care during severe infections (especially respiratory infections)	(lifestyle)	The ITIH2 pathway is most 'activated' in the kinds of high-inflammation states where time to treatment matters (severe COVID-19, sepsis). The safest strategy is early support before inflammation escalates.

ANIMAL Strictly Avoid

Using sincalide or other ITIH2-targeting drugs outside a clinical context	(pharmaceutical)	Evidence for ITIH2 inhibition is currently from cancer-model research, not prevention or general use; benefits/risks for healthy carriers are not documented.

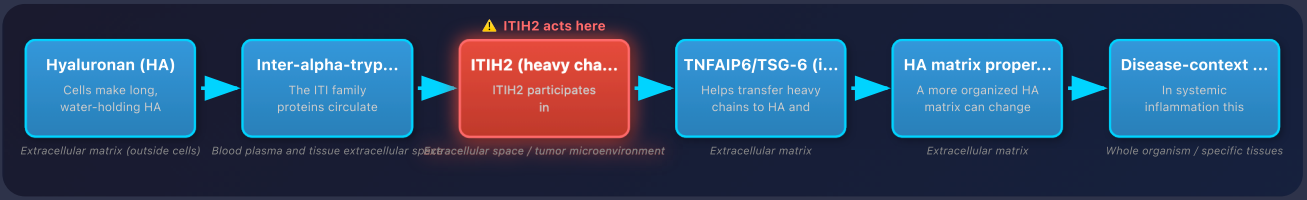
Foamy urine, blood in urine, new ankle/eye swelling, or unexplained high blood pressure	In lupus studies, urine ITIH2 correlated with disease activity and kidney involvement, highlighting that kidney inflammation can be 'silent' until it's advanced.	*Action: Arrange prompt evaluation with primary care; ask for urinalysis and kidney function labs.*

7. Key Biological Pathway

Hyaluronan (HA) matrix stabilization by the inter-alpha-trypsin inhibitor (ITI) family

Why this matters: This is the central 'why it matters' pathway for ITIH2 because the papers repeatedly connect ITIH2 to hyaluronan-associated remodeling in inflammation (sepsis, lupus activity, preeclampsia, COVID-19) and to tumor microenvironment behavior (cell migration/invasion). In plain terms: ITIH2 helps regulate how the body builds and tunes the gel-like extracellular matrix during stress, which can influence swelling, barrier function, immune cell traffic, and (in cancer settings) invasion.

Your tissues aren't just cells—they're cells sitting in a gel-like support matrix. Hyaluronan is a big part of that gel, and ITIH2 is one of the proteins that helps "reinforce" it so it's stable and organized. During inflammation or injury, the body remodels this gel; if that remodeling is unbalanced, you can get excess leakage/swelling, abnormal scarring, or (in tumors) a matrix that helps cancer cells move.



When this pathway is impaired:

Not documented in reviewed literature for rs151229507 specifically. From pathway evidence, the most plausible issue—if the variant altered ITIH2 expression/function—would be a subtle shift in HA-matrix remodeling during major inflammatory stress or within a tumor microenvironment, which could change how tissues swell, heal, or (in cancer contexts) how easily cells migrate. This remains an inference, not proven for this variant.

Other Related Pathways

No metabolic pathways associated with ITIH2 in KEGG. This gene may be involved in protein complexes or signaling rather than metabolic pathways.

8. Emergency Protocol

Because ITIH2 is repeatedly linked to the body's response during severe infections (COVID-19, septic shock), your practical 'illness rule' is: act early. If you develop a significant infection, prioritize hydration, rest, and early medical advice—especially for breathing symptoms, persistent high fever, or rapid worsening. If you have signs of sepsis (confusion, fainting, very rapid breathing, severe weakness), treat it as an emergency. This guidance is not because rs151229507 is proven harmful, but because ITIH2 sits in an extracellular-matrix + inflammation system that becomes most important precisely when infections become severe.

Warning Signs:

- Trouble breathing, bluish lips, or oxygen saturation low if you measure it
- Confusion, extreme sleepiness, or inability to keep fluids down
- Fainting, severe dizziness, or signs of very low blood pressure
- Rapid worsening over hours to 1–2 days despite basic care

9. Protein Information

Protein Length	237 amino acids
Function	ITIH2 is a gene that plays an important role in keeping the material between our cells stable and in managing inflammation. When there are changes or variants that reduce the gene's normal activity (k
Subcellular Location	Location not specified
Known Variants	0

10. Key References

Key References

1. COHORT N=33 **A serum proteome signature to predict mortality in severe COVID-19 patients.** (2021) PMID:34226277
   Supports variant mechanism understanding
2. CASE SERIES N=29 **Plasma proteomics in septic shock and alcohol-related pancreatitis: a hyaluronan-centered approach.** (2025) PMID:40885913
   Supports variant mechanism understanding
3. CASE-CONTROL **Urine inter-alpha-trypsin inhibitor family-related proteins may serve as biomarkers for disease activity of lupus.** (2022) PMID:35870194
   Supports variant mechanism understanding
4. ANIMAL **Hyaluronan network remodeling by ZEB1 and ITIH2 enhances the motility and invasiveness of cancer cells.** (2025) PMID:40178908
   Supports variant mechanism understanding
5. CASE SERIES 209 CITES N=185 **Frequent expression loss of Inter-alpha-trypsin inhibitor heavy chain (ITIH) genes in multiple human solid tumors: a systematic expression analysis.** (2008) PMID:18226209
   Supports variant mechanism understanding
6. CASE-CONTROL N=46 **Maternal plasma proteome profiling of biomarkers and pathogenic mechanisms of early-onset and late-onset preeclampsia.** (2022) PMID:36351970
   Documents trigger: Pregnancy complicated by preeclampsia (late-onset)
7. COHORT N=96 **Multi-omics analysis of the cervical epithelial integrity of women using depot medroxyprogesterone acetate.** (2022) PMID:35533147
   Documents trigger: Depot medroxyprogesterone acetate (DMPA) contraceptive exposure (cervical tissue context)
8. COHORT N=620 **Genome-wide association study of genetic predictors of overall survival for non-small cell lung cancer in never smokers.** (2013) PMID:23704207
   Supports carrier phenotype information
9. CASE-CONTROL N=501 **Plasma extracellular vesicle long RNA profiling identifies a diagnostic signature for the detection of pancreatic ductal adenocarcinoma.** (2020) PMID:31562239
   Supports Age- and sex-appropriate cancer screening (standard-of-care, individualized) monitoring

TLR10 — Full Report

1. Variant Information

Gene	TLR10
Variant ID	rs187892716
Protein Change	p.K3R
Genotype	G/T
ClinVar Classification	Not Applicable
Pathogenicity Score	16
Predicted Phenotype	Likely carrier

2. Associated Diseases

Prostate cancer (small increased genetic risk signal in a TLR region)

Some inherited differences in the TLR6–TLR1–TLR10 region were linked to a modestly higher chance of prostate cancer in a large Swedish case-control study, possibly through chronic inflammation pathways.

For carriers: Potentially relevant, but the paper did not study rs187892716 specifically and the signal reflects a region/haplotype rather than your exact variant; treat as a small risk modifier, not a diagnosis. (Paper 2).

H. pylori infection susceptibility

A meta-analysis found that one TLR10 variant (rs10004195 A>T) was associated with *protection* against H. pylori infection, suggesting TLR10 genetics can influence who is more/less likely to acquire this chronic stomach infection.

For carriers: Relevant as a concept (TLR10 variants can shift infection risk), but not directly transferable to rs187892716. (Paper 3).

Chronic gastritis inflammation tendency

In people with chronic gastritis, a TLR10 polymorphism (rs10004195) was associated with different patterns and severity of stomach lining inflammation.

For carriers: Only indirectly relevant—different SNP than yours; suggests TLR10 variation can influence inflammatory “style” in the stomach. (Paper 7).

Complications during severe bacterial infections

In Angolan children with pneumococcal meningitis, certain TLR10 variants were linked to differences in complications (like pneumonia, neurologic symptoms, blindness risk) and inflammatory markers in spinal fluid.

For carriers: Only indirectly relevant—different SNP set than yours and focused on children with confirmed meningitis; it does show TLR10 variation can affect outcomes during severe infection. (Paper 24).

Rheumatoid arthritis (risk or severity modifiers)

Some TLR10 variants have been associated with rheumatoid arthritis risk in a case-control study, and a specific functional coding variant (I473T) was linked to more erosive disease and poorer response to infliximab in certain RA patients.

For carriers: Indirect for rs187892716; most useful takeaway is that TLR10 can influence inflammatory pathway strength and treatment response when autoimmune disease is present. (Papers 20, 10/11).

3. Variant Mechanism

TLR10 is a “sensor-and-brake” on your early immune system (innate immunity). Think of other Toll-like receptors as smoke alarms that detect germs and then pull a fire alarm (inflammation). TLR10 seems to work more like a built-in “volume knob” or “brake,” dialing down inflammatory signaling from other TLRs so the response is strong enough to fight infection but not so strong that it causes excessive inflammation. This specific SNP (rs187892716) has an unknown protein change, and none of the reviewed papers directly studied rs187892716. So we can’t say with confidence whether your G/T result makes TLR10 more active, less active, or unchanged—this is **not documented in reviewed literature**. What we *can* do is use the broader TLR10 research to explain what kinds of downstream effects might matter if TLR10 signaling is shifted up or down.

Evidence Summary: Across multiple studies, TLR10 is repeatedly described as a regulator of inflammation: it can suppress broad TLR-driven cytokine production (suggesting an anti-inflammatory role), and certain functional coding variants can reduce this inhibitory effect and lead to higher NF-κB inflammatory activity. In immune cells like neutrophils and plasmacytoid dendritic cells, TLR10 levels and engagement influence movement toward infection signals (chemotaxis) and antiviral cytokine responses. Separately, several different TLR10 polymorphisms (not rs187892716) have been associated with infection susceptibility or inflammatory disease features (e.g., H. pylori infection, bacterial meningitis outcomes, rheumatoid arthritis susceptibility/prognosis, COVID-19 severity), supporting the idea that altering TLR10 function can “tilt” risk toward either infection susceptibility or inflammatory overactivity depending on direction of effect. (Papers: 9, 10/11, 4, 19, 3, 24, 20, 17, 5, 23, 15, 18).

4. Carrier Phenotype

With a **heterozygous (G/T)** result for rs187892716, you have one copy of the variant and one typical copy. For most immune-related SNPs, this usually means any effect—if there is one—is modest and shows up as a *tilt* in how strongly you react to infections or inflammation, not a clear-cut disease. Important nuance: none of the reviewed papers studied **rs187892716** specifically, and the protein change is unknown. So we cannot say that carriers of *this* exact SNP have a defined symptom pattern—this is **not documented in reviewed literature**. What carriers *may* want to pay attention to (based on broader TLR10 biology) is their personal pattern over time: do they tend to get unusually prolonged inflammatory symptoms after infections (suggesting a 'brake' that's a bit weaker), or do they feel they catch infections easily (suggesting immune coordination differences). Those are not guaranteed by your genotype, but they're reasonable self-observations to guide prevention and early care.

Can be symptomatic: Unknown/Rarely

Symptom frequency: Unknown

5. Documented Triggers

Bacterial products such as LPS (endotoxin) exposure/strong innate immune stimulation (2022)

In neutrophils, LPS activation (a strong bacterial signal sensed via TLR4) caused TLR10 expression changes and movement within the cell, showing that strong bacterial-pattern stimulation is a context where TLR10 regulation matters. Separately, LPS stimulation experiments show that having more functional TLR10 can blunt cytokine release, acting like a brake on an over-strong inflammatory response.

Viral stimulation (DNA and RNA viruses) (2024)

In plasmacytoid dendritic cells (the body's 'antiviral alarm' cells), engaging TLR10 with an antibody reduced cytokine production in response to DNA and RNA viruses and altered IRF7 signaling. That tells us that during viral illnesses, TLR10 can meaningfully tune the immune response.

Reactive oxygen species (ROS) / oxidative stress conditions (e.g., hypoxia-related ROS) (2010)

In THP-1 monocytes, hypoxia increased intracellular ROS and upregulated TLR10; adding hydrogen peroxide also increased TLR10, largely through NF-κB. In neutrophils, ROS depletion reduced TLR10 expression after LPS. So oxidative stress is a documented driver of TLR10 expression dynamics, which may matter if your baseline TLR10 function is shifted by genetics.

Vitamin D (active 1,25-dihydroxyvitamin D3) exposure (2014)

In THP-1 monocytes, active vitamin D increased surface and mRNA TLR10 expression (while reducing TLR2/4/5), suggesting vitamin D status could shift the 'TLR10 brake' availability in certain immune cells. This

is mechanistic cell-line evidence rather than a proven clinical trigger.

6. Evidence-Based Recommendations

Lifestyle

REVIEW ANIMAL

Prioritize consistent sleep and recovery—especially around infections.

IN VITRO

Treat 'high inflammatory load' days gently: if you're sick, give yourself permission to rest early rather than push through.

Diet

REVIEW ANIMAL

Aim for a generally anti-inflammatory eating pattern (plenty of fiber-rich plants; limit highly processed foods most days).

META-ANALYSIS

If you have chronic stomach symptoms (burning, nausea, early fullness), consider asking your clinician about H. pylori testing rather than self-treating long-term.

Exercise

IN VITRO

Keep exercise regular but avoid 'all-out' training when you're actively fighting an infection.

IN VITRO

If you notice you're slow to recover after hard workouts (extra soreness, prolonged 'inflammatory' feeling), experiment with more Zone 2 / moderate-intensity sessions and fewer maximal-effort days.

Supplements

IN VITRO

Vitamin D (discussion with clinician; test first) : Consider checking a 25(OH)D blood level and, if low, supplementing to reach a normal range with your clinician's guidance.

Pharmaceuticals

Important: Consult your doctor before starting any medication.

CASE-CONTROL 45 CITES N=3356

If you ever develop rheumatoid arthritis and infliximab is

Labs to Check

IN VITRO

: Active vitamin D can upregulate TLR10 expression in a monocyte cell model, suggesting

		being considered, it may be worth mentioning that certain functional TLR10 variants have been linked to a lower infliximab response and higher NF-κB activity in lab testing. This is not about rs187892716 specifically, so it should be treated as 'context for discussion,' not a decision-maker.	
Infliximab	(TNF inhibitor (biologic DMARD))		Side effects (significant): Infection risk (including serious infections), infusion reactions, rare immune/autoimmune complications; exact risks depend on individual factors.

25-hydroxyvitamin D [25(OH)D] blood level		vitamin D status could influence how available the 'TLR10 brake' is in some contexts. This is mechanistic evidence, not proven clinical benefit, but testing is low-risk and commonly used.	*(Frequency: Not documented in reviewed literature (commonly checked periodically based on clinical context).)*

CASE-CONTROL N=542

C-reactive protein (CRP)		: A TLR10 polymorphism (rs11725309 CT) was associated with higher CRP in RA patients, and TLR10 broadly regulates inflammatory signaling; CRP is a simple way to track systemic inflammation if you have symptoms.	*(Frequency: Not documented in reviewed literature (use symptom- or clinician-guided monitoring).)*

Symptoms to Watch

CASE SERIES N=25 SOON

Infections that feel unusually frequent, severe, or slow to resolve (especially		If TLR10 function were shifted toward less effective immune coordination (direction unknown for your SNP), you might notice more trouble 'turning the corner' on infections. The XLA gene-expression study suggests TLR10 hypo-expression could relate to	*Action: If you notice a pattern (e.g., repeated infections in a season, needing multiple antibiotics, or prolonged fevers), bring it to your clinician and mention your interest in innate-immune regulation/TLR10. Consider evaluation for common*

Things to Avoid

REVIEW ANIMAL Caution

Pushing through intense work/exercise	(lifestyle)	During acute infection your TLR pathways are already firing; TLR10 is part of the regulatory circuitry that tunes cytokine output. Extra physiologic stress may add inflammatory load. Direct	

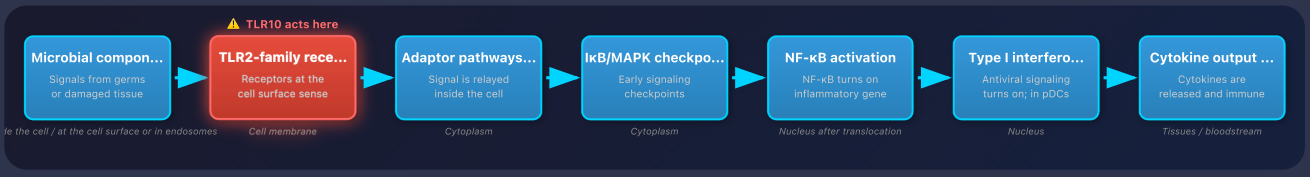
respiratory infections)	infection susceptibility, and immune-cell studies show TLR10 helps regulate responses to viral stimuli.	*reversible factors (sleep, vitamin D, exposures) and standard immune workup if clinically indicated.*	**while febrile or acutely ill**	evidence for rs187892716 is not documented in reviewed literature, so treat this as a precaution grounded in mechanism. (Papers 19, 5, 23).

7. Key Biological Pathway

TLR signaling "volume control" (MyD88/TRIF → NF-κB & interferon pathways)

Why this matters: This is the central reason TLR10 matters: it sits at the top of the immune alarm system and helps decide how loud the inflammatory signal should be. If TLR10's braking function is weaker, NF-κB-driven inflammation can run hotter; if TLR10 signaling/expression is lower, parts of early defense/coordination may be less well-tuned. This same pathway shows up in functional studies (TLR10 suppressing cytokines and NF-κB) and helps explain why TLR10 polymorphisms are linked to both infection outcomes and inflammatory disease features. (Papers 9, 10/11, 19, 5, 23).

When your immune system detects germs, it sends rapid "danger texts" (cytokines) to call in help. NF-κB and interferon pathways are the phone lines that broadcast those texts. TLR10 seems to help keep those messages proportionate—enough to clear infection without causing unnecessary tissue inflammation.



When this pathway is impaired:

Because rs187892716's functional effect isn't documented in the reviewed literature, we can't say exactly what changes. But in general: if TLR10's 'brake' function is reduced, NF-κB signaling and cytokine output may be higher, which could nudge toward chronic inflammation or stronger inflammatory reactions. If TLR10 expression/function is reduced in ways that impair immune coordination, it may tilt toward infection susceptibility or less controlled responses. (Papers 9, 10/11, 4, 19, 5, 23).

Other Related Pathways

No metabolic pathways associated with TLR10 in KEGG. This gene may be involved in protein complexes or signaling rather than metabolic pathways.

8. Emergency Protocol

If you develop a significant infection (high fever, shaking chills, trouble breathing, confusion, dehydration, or you feel rapidly worse), treat it as a situation where your innate immune pathways are under heavy load. Because TLR10 helps regulate inflammatory signaling and antiviral responses, the safest approach is early assessment rather than waiting it out. Stay hydrated, rest, and seek timely medical evaluation if symptoms escalate. If you have a history of severe infections or immune problems, discuss an individualized 'sick-day plan' with your clinician. Not documented in reviewed literature: a TLR10-specific emergency protocol, thresholds, or medication plan.

Warning Signs:

- Shortness of breath
- Chest pain
- Confusion or fainting
- Persistent high fever
- Signs of dehydration (very low urine output, dizziness)

9. Protein Information

Protein Length	811 amino acids
Function	TLR10 is a gene that normally acts as a brake on the immune system, helping to keep inflammation under control. When there are loss-of-function changes—mutations that lower or stop the gene's normal a
Subcellular Location	Location not specified

Known Variants	0

10. Key References

Key References

1. ANIMAL **TLR10 Is a Negative Regulator of Both MyD88-Dependent and -Independent TLR Signaling.** (2016) PMID:27022193
   Supports variant mechanism understanding
2. CASE-CONTROL 45 CITES N=3356 **A functional variant of TLR10 modifies the activity of NFkB and may help predict a worse prognosis in patients with rheumatoid arthritis.** (2016) PMID:27716427
   Supports variant mechanism understanding
3. IN VITRO **Regulation of TLR10 Expression and Its Role in Chemotaxis of Human Neutrophils.** (2022) PMID:35613551
   Supports variant mechanism understanding
4. IN VITRO **TLR10 (CD290) Is a Regulator of Immune Responses in Human Plasmacytoid Dendritic Cells.** (2024) PMID:38995177
   Supports variant mechanism understanding
5. REVIEW ANIMAL **TLR10: Insights, controversies and potential utility as a therapeutic target.** (2021) PMID:33047375
   Supports variant mechanism understanding
6. REVIEW ANIMAL **TLR10 and Its Role in Immunity.** (2022) PMID:34595581
   Supports variant mechanism understanding
7. IN VITRO **Reactive oxygen species enhance TLR10 expression in the human monocytic cell line THP-1.** (2010) PMID:21152300
   Documents trigger: Reactive oxygen species (ROS) / oxidative stress conditions (e.g., hypoxia-related ROS)
8. IN VITRO **1,25-Dihydroxyvitamin D3 up-regulates TLR10 while down-regulating TLR2, 4, and 5 in human monocyte THP-1.** (2014) PMID:24373795
   Documents trigger: Vitamin D (active 1,25-dihydroxyvitamin D3) exposure
9. META-ANALYSIS **Association between genetic polymorphisms and host susceptibility to Helicobacter pylori infection: a systematic review and meta-analysis.** (2025)

PMID:41337555

Supports diet: If you have chronic stomach symptoms (burning, nau...

10. CASE-CONTROL N=542 **Analysis of TLR10 gene polymorphisms in patients with rheumatoid arthritis.** (2024) PMID:38941669
    Supports C-reactive protein (CRP) monitoring
11. CASE SERIES N=25 **Dysregulation of Toll-Like Receptor Signaling-Associated Gene Expression in X-Linked Agammaglobulinemia: Implications for Correlations Genotype-Phenotype and Disease Expression.** (2024) PMID:39116841
    Documents symptom: Infections that feel unusually frequent, severe, or slow to resolve (especially respiratory infections)
12. **Joint influences of Acidic-Mammalian-Chitinase with Interleukin-4 and Toll-like receptor-10 with Interleukin-13 in the genetics of asthma.** (2010) PMID:20444155
    PRS correlation: Asthma - A haplotype-based candidate-gene analysis in asthmatic children vs controls reported that TLR10 vari
13. **Analyses of associations with asthma in four asthma population samples from Canada and Australia.** (2009) PMID:19247692
    PRS correlation: Asthma - A haplotype-based candidate-gene analysis in asthmatic children vs controls reported that TLR10 vari

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TMEM59 — Full Report

1. Variant Information

Gene	TMEM59
Variant ID	rs200790405
Protein Change	p.C2I
Genotype	C/T
ClinVar Classification	Not Applicable
Pathogenicity Score	16

Predicted Phenotype	Likely carrier

2. Associated Diseases

Post-stroke inflammation sensitivity

After a stroke, brain immune cells can overreact and worsen secondary injury. TMEM59 levels in microglia influence how intense that inflammatory response becomes in models.

For carriers: No direct human carrier-risk data for rs200790405. Evidence is from mouse and cell models showing TMEM59 loss worsens outcomes; whether your C/T variant changes TMEM59 is not documented. (Paper 3, 2021; Paper 1, 2025)

Amyloid pathology modulation (research)

In Alzheimer's mouse models, higher TMEM59 levels track with disease stages, and reducing TMEM59 by one copy improved amyloid plaque-related changes and memory in mice.

For carriers: Haploinsufficiency in mice (one less functional copy) was beneficial in models, but this does not prove protection in humans or for this specific SNP. Not documented in reviewed literature for rs200790405. (Paper 15/16, 2020)

Tau pathology modulation (research)

In a tauopathy mouse model, TMEM59 levels increased with pathology; reducing TMEM59 improved cognitive deficits and disease-like changes, linked to increased chaperone-mediated autophagy.

For carriers: Mouse haploinsufficiency/deficiency suggests lowering TMEM59 can be beneficial in that model, but human carrier implications are unknown. Not documented in reviewed literature for rs200790405. (Paper 8, 2025)

Inflammation-linked smell loss (research)

In mice, deleting TMEM59 reduced olfactory neuron maintenance and regeneration and increased inflammatory cell infiltration; anti-inflammatory treatment improved function in the KO animals.

For carriers: Evidence involves full gene deletion in mice. Whether a heterozygous human carrier has smell changes is not documented in reviewed literature. (Paper 13, 2023)

Microglia/synapse pruning differences (research)

TMEM59 expression was reported as decreased in autistic patients, and mouse loss (including microglia-specific loss) was studied in relation to synaptic pruning and behavior in that work.

For carriers: The paper snippet suggests human expression differences but does not tie rs200790405 to ASD risk, and details are incomplete here. Not documented in reviewed literature for this specific variant. (Paper 14, 2022)

3. Variant Mechanism

TMEM59 is a small membrane protein that sits in cell membranes (often in the Golgi/endosome system) and helps coordinate how cells traffic proteins, tune certain immune/inflammation responses, and run specific types of “cell cleanup” (autophagy). A helpful analogy: think of TMEM59 as a traffic controller and quality-control tagger inside cells—helping decide what gets routed where and what gets sent to the recycling/cleanup system. Across the papers, TMEM59 shows up repeatedly in brain-support cells (microglia) and other tissues as a regulator of inflammation pathways (like NF-κB) and inflammatory cell death (pyroptosis), and as a partner in selective/unconventional autophagy via ATG16L1 binding. It also influences complex glycosylation (how sugar chains are added to proteins) and can change how APP (amyloid precursor protein) is processed and trafficked. How your specific variant affects this: the reviewed papers do not study rs200790405 directly, and the protein change is unknown. That means we cannot say whether this C/T change increases or decreases TMEM59 function in your body. Not documented in reviewed literature.

Evidence Summary: What we can say with confidence from the literature is what TMEM59 does when it is experimentally increased, decreased, or deleted: - In stroke models, TMEM59 appears protective: lowering or knocking out TMEM59 makes microglia more inflammatory and increases pyroptosis and brain injury, while raising TMEM59 reduces pyroptosis and inflammation (mouse + cell models). (Paper 3, 2021; Paper 1, 2025) - In Alzheimer’s/tauopathy mouse models, having less TMEM59 (haploinsufficiency/deficiency) improved pathology and cognition, while TMEM59 is increased at pathological stages and overexpression can be harmful in these models. (Paper 15/16, 2020; Paper 8, 2025) - TMEM59 also interacts with TREM2 and helps regulate microglial autophagy, metabolism, and inflammatory tone; changing TMEM59 levels can partially “rescue” abnormalities in Trem2-deficient microglia. (Paper 4/5, 2020) - TMEM59 promotes Wnt signaling by helping receptors cluster into “signalosomes,” which is a core communication pathway for cell fate and tissue maintenance. (Paper 17/18, 2018) - TMEM59 contains an ATG16L1-binding motif that locally activates LC3 tagging on endosomes (a selective/unconventional autophagy process), including during bacterial infection; this process can be disrupted when ATG16L1 carries the Crohn-risk T300A polymorphism. (Paper 22, 2013; Paper 20, 2016) For you as a heterozygous carrier (C/T): there is no direct evidence in these papers that heterozygous carriers of rs200790405 have symptoms, higher disease risk, or a specific clinical syndrome. The closest evidence to “heterozygous-like” effects comes from mouse haploinsufficiency studies (having one working copy), which showed benefit in Alzheimer’s/tauopathy models (less TMEM59 → less pathology). However, that is a disease-model context and not proof of benefit or risk in healthy human carriers. (Paper 15/16, 2020; Paper 8, 2025) Bottom line: your variant is best treated as a research finding with uncertain personal impact. The practical focus is supporting the biological systems TMEM59 participates in—brain immune balance, inflammation control, and cellular cleanup—especially during high-stress situations that push inflammation pathways. Not documented in reviewed literature for rs200790405-specific effects.

4. Carrier Phenotype

You carry one copy (C/T) of rs200790405 in TMEM59. Based on the papers provided, there is no direct evidence that heterozygous carriers of this specific variant develop a predictable set of symptoms. What *is* known is that TMEM59 is a 'dial' in immune/inflammation and cellular cleanup pathways—especially in microglia. In disease models, turning the dial down (or removing TMEM59) can be harmful in stroke settings (more inflammatory cell death), but turning the dial down can be helpful in Alzheimer's/tauopathy models (less protein-aggregation pathology). That mixed direction is a big clue that the "right" TMEM59 level is context-dependent, and it's why we can't assume your variant is good or bad without rs200790405-specific functional data. Practically, as a carrier, the safest interpretation is: you likely do not need disease-specific treatment, but it's reasonable to be proactive about inflammation control and brain-health habits—because those are the systems TMEM59 is repeatedly involved in across studies. Not documented in reviewed literature that rs200790405 changes TMEM59 expression or activity.

Can be symptomatic: Unknown/Rarely

Symptom frequency: Unknown

5. Documented Triggers

Ischemia/reperfusion-like stress (e.g., stroke models; oxygen-glucose deprivation/reoxygenation in cells) (2021)

In mouse and microglial-cell models, ischemia/reperfusion stress lowers TMEM59 in microglia and strongly activates pyroptosis/inflammation. When TMEM59 is knocked out, injury and inflammatory pyroptosis markers rise; increasing TMEM59 blunts this. This matters because it shows TMEM59 is part of the brain's 'damage control' system during extreme metabolic stress. (Paper 3, 2021)

LPS-driven inflammatory stress (bacterial-toxin immune activation) (2020)

Lipopolysaccharide (LPS) exposure decreases TMEM59 expression and is used to model strong innate immune activation. In microglia studies, altering TMEM59 levels changes inflammatory outputs; in mastitis models/cells, TMEM59 was part of an anti-inflammatory mechanism targeted by a plant extract component. This matters because it ties TMEM59 to how your cells respond to strong infection-like inflammatory signals. (Paper 4/5, 2020; Paper 2, 2024)

Staphylococcus aureus infection (autophagy/xenophagy context) (2013)

Endogenous TMEM59 interacts with ATG16L1 and helps drive LC3 'tagging' and lysosomal targeting of TMEM59-positive endosomes during Staphylococcus aureus infection. This matters because it connects

TMEM59 to the cell's targeted cleanup/defense response to certain bacteria. (Paper 22, 2013)

Aging-related tissue changes (brain/taste papilla/olfactory epithelium) (2023)

Several single-cell and animal studies report TMEM59 is downregulated with aging in certain tissues (taste papilla, olfactory epithelial lineages), and TMEM59 deletion worsens inflammation-linked degeneration in the olfactory system. This matters because age-related inflammation ('inflamm-aging') is a context where TMEM59 regulation appears relevant. (Paper 11, 2024; Paper 13, 2023)

Hypobaric pressure exposure (experimental anti-senescence condition) (2026)

A 2026 study reports hypobaric pressure activates TMEM59 to induce lysosome-dependent cell death in senescent cells. This is a very specific experimental exposure, and there is no guidance here about real-world safety or clinical use. (Paper 7, 2026)

6. Evidence-Based Recommendations

Lifestyle

ANIMAL

Treat inflammation recovery like a daily priority: aim for a consistent sleep schedule (same wake time, 7–9 hours) and build in a short wind-down routine.

IN VITRO

Have a 'when I'm sick' plan: if you get a significant infection (high fever, severe flu-like illness), prioritize rest, hydration, and early medical advice—especially if you notice confusion, unusual weakness, or severe headache.

ANIMAL

Be cautious with DIY 'extreme environment' experiments (e.g., aggressive hypobaric/pressure protocols) unless supervised in a research/clinical setting.

Diet

IN VITRO 27 CITES

Use a Mediterranean-leaning pattern most days: vegetables/legumes, nuts/olive oil, fish 2x/week, and keep ultra-processed foods as an occasional item.

Exercise

Aim for steady, moderate activity (e.g., brisk walking/cycling) most days, and treat "recovery" as part of training (easy day after hard day).

Supplements

ANIMAL

Isochlorogenic acid B (ICAB) / Rhapontici Radix extract components : Do not self-prescribe these specifically for TMEM59. If you're already considering herbal anti-inflammatories,

discuss safety and interactions with a clinician/pharmacist first.

Pharmaceuticals

Important: Consult your doctor before starting any medication.

ANIMAL

Dexamethasone (context: anti-inflammatory steroid)	(glucocorticoid)	Not a daily prevention strategy. The key takeaway is that anti-inflammatory treatment reversed olfactory problems in TMEM59-knockout mice after injury; in real life, steroids have meaningful risks and are only for specific medical situations. If you ever have a severe inflammatory ENT issue with smell loss, this paper is a reason to ask an ENT whether inflammation is a driver and what evidence-based treatments are appropriate.	Side effects (significant): Can raise blood sugar, worsen sleep/mood, increase infection risk, and cause bone and muscle effects with repeated or high-dose use. Not detailed in the reviewed literature.

Labs to Check

Blood pressure, fasting lipids, HbA1c/fasting glucose (routine cardiometabolic monitoring)	: TMEM59-related research is strongest in stroke models, where vascular risk factors drive overall stroke risk more than any single gene. While these tests are not TMEM59-specific, they are practical levers to reduce the main trigger context (ischemic events) studied in the TMEM59 stroke papers. Not documented in reviewed literature as TMEM59-specific monitoring.	*(Frequency: At routine intervals based on age/risk with your primary care clinician (often yearly).)*

ANIMAL 14 CITES

Clinical cognitive screening if you notice persistent changes (memory, word-finding, navigation)	: TMEM59 is implicated in Alzheimer's/tauopathy model pathology modulation, but no rs200790405 carrier guidance exists. Monitoring is symptom-driven and pragmatic rather than gene-driven here. Not documented in reviewed literature as a TMEM59-carrier screening protocol. (Paper 15/16, 2020; Paper 8, 2025)	*(Frequency: If symptoms arise; otherwise at standard wellness visits if you're concerned.)*

Symptoms to Watch

ANIMAL EMERGENCY

Sudden one-sided weakness, face droop, trouble speaking, sudden severe headache, or sudden vision changes	These are classic stroke warning signs. TMEM59 is part of the inflammation/pyroptosis response after ischemia in models, but the key point is: time matters most for treatment in real life.	*Action: Call emergency services immediately (do not drive yourself).*

ANIMAL SOON

New or worsening loss of smell, especially after a viral illness or nasal inflammation	TMEM59 deletion in mice caused olfactory neuron loss and inflammation; inflammation treatment improved function in that model, suggesting smell loss can be inflammation-linked in TMEM59 pathways (in mice).	*Action: If it persists beyond ~2–4 weeks or is severe, consider evaluation with primary care/ENT, especially if accompanied by sinus symptoms.*

Things to Avoid

ANIMAL Avoid

Self-directed hypobaric/pressure protocols marketed for anti-aging	(lifestyle)	TMEM59 can be activated by hypobaric pressure in experimental settings to drive lysosome-dependent cell death. The human safety/benefit of replicating this is not established in the reviewed literature, so it's better treated as 'research only' for now.

ANIMAL Avoid

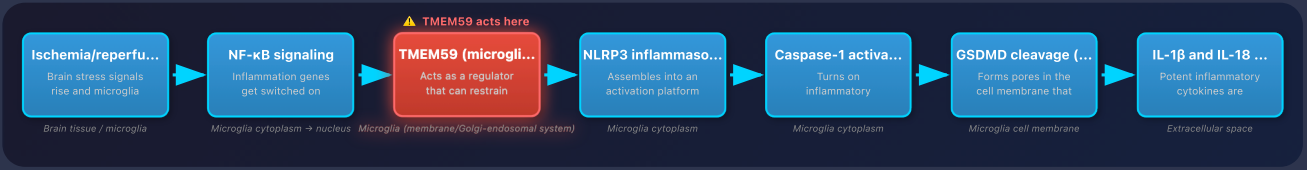
Using systemic steroids (e.g., dexamethasone) casually for minor symptoms	(pharmaceutical)	Although steroids helped TMEM59-KO mice in an olfactory injury model, systemic steroids carry significant side effects and should be reserved for clear medical indications.

7. Key Biological Pathway ⓘ

🔬 **Microglial inflammasome/pyroptosis control (NLRP3 → Caspase-1 → IL-1β/IL-18) with NF-κB "priming"**

Why this matters: This is the most consistent, directly tested mechanism connecting TMEM59 levels to a meaningful health outcome in the reviewed literature: when TMEM59 is reduced or absent, microglia become more inflammatory and more prone to pyroptosis after ischemia/reperfusion stress; when TMEM59 is increased, pyroptosis and neuroinflammation are reduced. This pathway explains why TMEM59 is repeatedly discussed in stroke/neuroinflammation papers and why "inflammatory stress" is the most relevant trigger theme here. (Paper 3, 2021; Paper 1, 2025)

Microglia are the brain's immune "housekeepers." When they sense danger (like low oxygen during stroke), they can flip into an emergency mode that releases strong inflammatory signals—and sometimes they self-destruct in a fiery way called pyroptosis. TMEM59 seems to act like a brake that helps keep that emergency response from overshooting. (Paper 3, 2021)



When this pathway is impaired:

When TMEM59 is experimentally knocked out or suppressed in these models, the NF-κB response and pyroptosis markers (NLRP3, ASC, cleaved caspase-1, GSDMD-N, mature IL-1β/IL-18) increase, microglia activation rises, and stroke outcomes worsen. If a person's variant reduced TMEM59 function (not proven for rs200790405), the theoretical vulnerability would be an easier "overshoot" of inflammatory responses during major brain stress. (Paper 3, 2021; Paper 1, 2025)

Other Related Pathways

No metabolic pathways associated with TMEM59 in KEGG. This gene may be involved in protein complexes or signaling rather than metabolic pathways.

8. Emergency Protocol

If you develop a significant infection (high fever, severe systemic symptoms), prioritize rest, hydration, and early medical evaluation rather than "pushing through." TMEM59 is involved in how cells handle strong inflammatory signals (LPS models) and in selective autophagy responses during bacterial infection models; while we don't know your variant's functional direction, avoiding prolonged, unmanaged inflammatory stress is a sensible precaution. If you have neurologic red flags (confusion, new weakness, trouble speaking, severe headache) during illness, treat that as urgent/emergency.

Warning Signs:

- Confusion or new disorientation
- New one-sided weakness/numbness

- Trouble speaking or understanding
- Severe headache unlike usual
- Severe dehydration (not keeping fluids down)

9. Protein Information

Protein Length	239 amino acids
Function	TMEM59 is a gene responsible for making a protein that plays key roles in how cells communicate, clean themselves up, and process other proteins. When the gene doesn't work as it should (a loss of fun
Subcellular Location	Location not specified
Known Variants	0

10. Key References

Key References

1. ANIMAL **TMEM59 protects against cerebral ischemic stroke by suppressing pyroptosis and microglial activation.** (2021) PMID:33517129
   Supports variant mechanism understanding
2. ANIMAL **HOXA5 Inhibits Microglia Pyroptosis in Cerebral Stroke by Regulating FTO-Mediated TMEM59 m** (2025) PMID:40772328
   Supports variant mechanism understanding
3. ANIMAL 14 CITES **TMEM59 Haploinsufficiency Ameliorates the Pathology and Cognitive Impairment in the 5xFAD Mouse Model of Alzheimer's Disease** (2020) PMID:33195275
   Supports variant mechanism understanding

4. ANIMAL **TMEM59 deficiency activates chaperone-mediated autophagy and ameliorates disease-like pathologies in tauopathy model mice.** (2025) PMID:40551290
   Supports variant mechanism understanding
5. IN VITRO **TMEM59 defines a novel ATG16L1-binding motif that promotes local activation of LC3.** (2013) PMID:23376921
   Supports variant mechanism understanding
6. IN VITRO **Unconventional autophagy mediated by the WD40 domain of ATG16L1 is derailed by the T300A Crohn disease risk polymorphism.** (2016) PMID:27541200
   Supports variant mechanism understanding
7. IN VITRO 46 CITES **TMEM59 potentiates Wnt signaling by promoting signalosome formation** (2018) PMID:29632210
   Supports variant mechanism understanding
8. IN VITRO 27 CITES **TMEM59 interacts with TREM2 and modulates TREM2-dependent microglial activities.** (2020) PMID:32826884
   Supports variant mechanism understanding
9. IN VITRO 71 CITES **The novel membrane protein TMEM59 modulates complex glycosylation, cell surface expression, and secretion of the amyloid precursor protein.** (2010) PMID:20427278
   Supports variant mechanism understanding
10. ANIMAL **TMEM59 ablation leads to loss of olfactory sensory neurons and impairs olfactory functions via interaction with inflammation.** (2023) PMID:37061103
    Documents trigger: Aging-related tissue changes (brain/taste papilla/olfactory epithelium)
11. ANIMAL **Intermittent hypobaric pressure induces selective senescent cell death and alleviates age-related osteoporosis.** (2026) PMID:41535389
    Documents trigger: Hypobaric pressure exposure (experimental anti-senescence condition)
12. ANIMAL **In vivo and in vitro anti-inflammation of Rhapontici Radix extract on mastitis via TMEM59 and GPR161.** (2024) PMID:38942158
    Supports Isochlorogenic acid B (ICAB) / Rhapontici Radix extract components recommendation

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SMIM22 — Full Report

1. Variant Information

Gene	SMIM22
Variant ID	rs778473760
Protein Change	p.H7A
Genotype	AG|A
ClinVar Classification	Not Applicable
Pathogenicity Score	14
Predicted Phenotype	Likely affected

2. Associated Diseases

Lung cancer prognosis marker (research)

In lung squamous cell carcinoma datasets, SMIM22 expression was part of a 3-gene risk model linked with overall survival.

For carriers: This is about SMIM22 levels in tumor tissue, not about carrying rs778473760. Not documented in reviewed literature that carriers have increased lung cancer risk. (PMID: 39711312)

Lung cancer growth pathway (research)

In lab and mouse xenograft models, SMIM22 helped drive glycolysis and proliferation, supporting NSCLC tumor growth when regulated by immune-cell EV signals.

For carriers: Mechanism shown in cell lines/xenografts; no evidence here that inherited rs778473760 predicts NSCLC risk or symptoms in carriers. (PMID: 39215037)

Liver cancer stemness program (research)

In a hepatocellular carcinoma cell line, SMIM22 was one of nine genes overexpressed in a stem-cell-like subpopulation, and forced expression of the set helped maintain tumor-forming ability in culture.

For carriers: In vitro cancer-cell findings; not evidence that carriers develop liver disease or liver cancer. Not documented in reviewed literature. (PMID: 37610679)

Prostate cancer recurrence predictor (research)

In TCGA prostate cancer data, SMIM22 was part of a 6-gene expression signature that predicted biochemical recurrence after surgery.

For carriers: This is a tumor expression signature, not a germline (inherited) variant association. Not documented in reviewed literature. (PMID: 30637711)

3. Variant Mechanism

SMIM22 is a very small, not-well-characterized human gene that shows up repeatedly in cancer research as a "tumor-behavior marker." Based on the papers you provided, SMIM22 seems to act like a tiny control knob that can influence how strongly cancer cells keep "stem-cell-like" features (the ability to self-renew and keep forming tumors) and how strongly they run glycolysis (a fast way of making energy from sugar). Analogy: Think of SMIM22 like a dimmer switch on a cancer cell's "growth mode." When SMIM22 is turned up, the cell is more likely to stay in an aggressive, self-renewing state and to favor sugar-burning (glycolysis) that supports rapid growth. How your variant might affect this: rs778473760 is a DNA-level variant, and the protein change is unknown here. None of the reviewed papers studied this exact variant or showed how inherited SMIM22 variants change SMIM22 function in healthy people. So we cannot say whether your genotype increases or decreases SMIM22 activity or meaningfully changes disease risk. Not documented in reviewed literature.

Evidence Summary: What the literature actually shows is about SMIM22 *expression* in tumors (how much SMIM22 RNA/protein a tumor makes), not about inherited SMIM22 variants. Across several cancers, higher SMIM22 expression is part of multi-gene signatures linked to worse outcomes or tumor "stemness," and in lab models forcing expression of SMIM22 (with other genes) helped maintain tumor-forming ability. In NSCLC lab/xenograft models, SMIM22 sits in a pathway that boosts glycolysis and tumor growth. These findings suggest SMIM22 can matter to tumor biology, but they do not prove that being born with rs778473760—whether heterozygous or homozygous—causes symptoms or increases cancer risk. Key take-home: treat this as a research signal about *tumor pathways* (especially glycolysis and pro-growth signaling), not as a confirmed inherited disease-causing variant. (Papers 1–5)

4. Carrier Phenotype

Right now, based on the papers you provided, there is no evidence that people who carry rs778473760 in SMIM22—whether heterozygous or homozygous—have a predictable set of symptoms. The literature you shared focuses on SMIM22 as a gene that tumors may turn up or down, and how that relates to tumor behavior. That's different from a classic 'single-gene disorder' where an inherited variant reliably causes a disease. So, for you as a homozygous carrier: treat this result as 'uncertain personal health impact.' It's reasonable to use it as motivation to optimize general cancer-risk-reduction habits and stay on top of age-appropriate screening, but it does not, by itself, diagnose anything. For a heterozygous carrier: same message—being a carrier is not shown here to cause symptoms or clearly raise cancer risk. Not documented in reviewed literature. (Papers 1–5)

Can be symptomatic: Unknown/Rarely

Symptom frequency: Unknown

5. Documented Triggers

Tumor-associated inflammation and M2 macrophage signaling (EV/lncRNA NORAD exposure) (2024)

In NSCLC models, signals packaged into extracellular vesicles from M2 macrophages (including lncRNA NORAD) increased SMIM22-related signaling and supported glycolysis and tumor growth. This is a 'trigger' in a tumor microenvironment sense (immune-cell signals pushing cancer growth), not a day-to-day trigger proven to affect healthy carriers.

Stem-cell-supporting culture conditions (mTeSR1 medium) in cancer cells (2023)

In a hepatocellular carcinoma cell line, a stem-cell-like culture medium maintained a tumor-forming subpopulation along with high expression of SMIM22 and other genes; changing conditions reduced those cells and gene expression. This is an experimental trigger in a lab model—not a documented lifestyle trigger for people.

6. Evidence-Based Recommendations

Lifestyle

COHORT

Treat this result as a 'cancer-biology awareness' flag: keep up with age-appropriate cancer screening and don't skip routine checkups.

Aim for steady, consistent sleep (most nights a similar bedtime/wake time).

Diet

ANIMAL 9 CITES

Favor a 'steady glucose' eating pattern most days (balanced meals with protein + fiber, and limit large sugar spikes).

Exercise

Keep exercise regular and moderate (e.g., brisk walking/cycling/strength training) and choose consistency over extremes.

Supplements

None found during research

Pharmaceuticals

None found during research

Labs to Check

COHORT N=358

Follow standard, guideline-based cancer screening for your age/sex (e.g., colon cancer screening; prostate screening discussions where appropriate; lung cancer screening only if you meet smoking history criteria).	: SMIM22 is repeatedly observed as a prognostic/biologic factor in multiple cancers, but there is no validated germline risk management protocol for rs778473760. The most evidence-aligned approach is not extra testing 'because of SMIM22,' but diligent adherence to standard screening so that if a cancer arises, it's caught early. (PMID: 39711312; PMID: 30637711)	*(Frequency: Per standard national guidelines and your clinician's plan (not variant-specific).)*

Symptoms to Watch

ANIMAL 9 CITES URGENT

Unexplained, persistent cough; coughing up blood; ongoing shortness of breath	SMIM22 is implicated in lung cancer biology and prognosis in the reviewed literature, but symptoms are not variant-specific. These are general warning signs where early evaluation matters.	*Action: If persistent beyond ~2–3 weeks, or if any blood is present, contact a clinician promptly; seek urgent care for severe breathing difficulty.*

COHORT N=358 SOON

New urinary obstruction symptoms or blood in urine; persistent	SMIM22 appears in a prostate cancer recurrence prediction signature (tumor expression). These symptoms	*Action: Schedule medical evaluation soon; go urgently if heavy*

Things to Avoid

COHORT Caution

Assuming this variant diagnoses a condition or guarantees increased cancer risk	(lifestyle)	The reviewed literature links SMIM22 to tumor expression patterns and experimental cancer biology. It does not establish rs778473760 as pathogenic or predictive for individuals. Over-interpreting could cause unnecessary anxiety or inappropriate testing. (Papers 1–5)

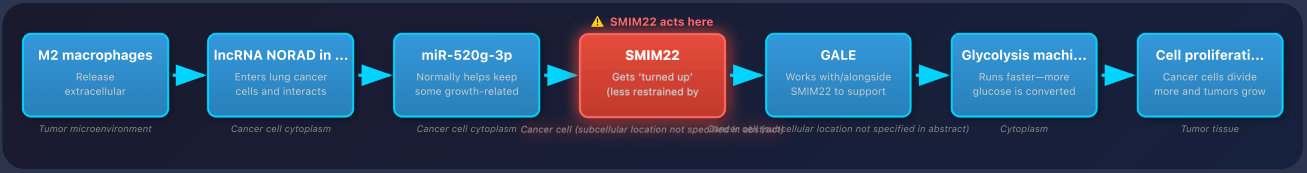
pelvic/bone pain in an at-risk person	aren't caused by the variant, but they are important to evaluate early.	*bleeding, inability to urinate, or severe pain.*

7. Key Biological Pathway

Cancer-cell "sugar-burning" (glycolysis) growth program linked to SMIM22/GALE

Why this matters: Across the provided literature, the clearest, most specific mechanism involving SMIM22 is its role in promoting glycolysis and cancer cell proliferation in NSCLC models, and its association with tumorigenicity in cancer stem-cell-like cells. Understanding this pathway helps you understand *what SMIM22 is doing in these studies* (supporting rapid-growth energy use), even though your inherited variant's effect is not established. (PMID: 39215037; PMID: 37610679)

Cells can make energy slowly and efficiently, or quickly and "expensively." Many cancers prefer the quick option—glycolysis—because it fuels fast growth. In the NSCLC model, SMIM22 acts like a helper that turns up this sugar-burning program (through a SMIM22/GALE axis), making tumor cells grow more easily. (PMID: 39215037)



When this pathway is impaired:

In the cancer models, when this program is overly active, cells are better at rapid growth and survival. Importantly, the reviewed papers do not show that inherited SMIM22 variants (including rs778473760) cause this pathway to be overactive in healthy tissues—this mechanism is documented mainly in tumor biology and experimental systems. (PMID: 39215037; PMID: 37610679)

Other Related Pathways

No metabolic pathways associated with SMIM22 in KEGG. This gene may be involved in protein complexes or signaling rather than metabolic pathways.

8. Emergency Protocol

No SMIM22-variant-specific emergency protocol is documented in the reviewed literature. If you have severe symptoms (chest pain, severe shortness of breath, coughing up blood, neurologic symptoms, or signs of severe infection), seek emergency care as you normally would.

Warning Signs:

- Coughing up blood
- Severe shortness of breath
- Chest pain/pressure
- Fainting or new confusion

9. Protein Information

Protein Length	135 amino acids
Function	SMIM22 is a gene that provides instructions to make a small protein embedded in the cell membrane. This protein plays important roles in controlling how cells use energy and how quickly they grow. Whe
Subcellular Location	Location not specified
Known Variants	0

10. Key References

Key References

1. COHORT **Identification of ALDH7A1 as a DNA-methylation-driven gene in lung squamous cell carcinoma.** (2025) PMID:39711312
   Supports variant mechanism understanding

2. IN VITRO 3 CITES **Identification of a gene set that maintains tumorigenicity of the hepatocellular carcinoma cell line Li-7** (2023) PMID:37610679
Supports variant mechanism understanding

3. ANIMAL 9 CITES **M2 macrophage-derived lncRNA NORAD in EVs promotes NSCLC progression via miR-520g-3p/SMIM22/GALE axis.** (2024) PMID:39215037
Supports variant mechanism understanding

4. COHORT N=358 **Identification a novel set of 6 differential expressed genes in prostate cancer that can potentially predict biochemical recurrence after curative surgery.** (2019) PMID:30637711
Supports variant mechanism understanding

KLHL35 — Full Report

1. Variant Information

Gene	KLHL35
Variant ID	rs756778027
Protein Change	p.T5D
Genotype	TCGGGCCGCCCGGCCGCGAACAAGCTG/T
ClinVar Classification	Not Applicable
Pathogenicity Score	14
Predicted Phenotype	Likely carrier

2. Associated Diseases

Alzheimer's necroptosis signature

In one study, KLHL35 was part of an eight-gene pattern that helped classify Alzheimer's disease subtypes linked to inflammatory cell death (necroptosis) and immune cell infiltration.

For carriers: Low/uncertain. This evidence is about gene expression patterns in Alzheimer's disease samples, not about inherited variants or carrier status. No carrier symptoms were described. (PMID: 38478169)

Colon cancer prognosis marker

Several studies found that KLHL35 expression helped predict outcomes in colon/colorectal cancer, where higher expression was generally linked to poorer survival or more advanced disease features in those datasets.

For carriers: Uncertain for carriers. These are tumor-tissue expression/prognosis studies and don't show that inheriting rs756778027 increases colon cancer risk. (PMID: 37158531; 35928453; 39920741; 41114922)

Head & neck cancer immune-death signature

KLHL35 contributed to a gene-expression signature related to pyroptosis (an inflammatory cell-death process) that stratified prognosis and immune features in head and neck cancer.

For carriers: Uncertain for carriers; this is a tumor-expression signature, not an inherited-risk study. (PMID: 36685979)

Lung cancer prognosis marker (TP53-mut group)

In a TP53-mut lung adenocarcinoma subgroup, higher KLHL35 expression correlated with better survival in the model described.

For carriers: Uncertain for carriers; again this is about tumor expression in a specific cancer subgroup. (PMID: 35116695)

Kidney cancer methylation marker

KLHL35 was frequently promoter-methylated in renal cell carcinoma samples and knockdown experiments suggested effects on growth behavior in a lab setting.

For carriers: Uncertain for carriers. This is about tumor methylation/silencing and lab knockdown, not inherited rs756778027. (PMID: 21132003)

3. Variant Mechanism

KLHL35 is part of the "kelch-like" protein family. Proteins in this family often act like adaptors—think of them as a cargo-hook that helps a cell's recycling system (the ubiquitin–proteasome system) decide which proteins should be tagged and broken down, and which should be left alone. This kind of protein-quality-control is especially important when cells are stressed, dividing, or responding to inflammation. For KLHL35 specifically, the reviewed papers don't provide a definitive, universally accepted description of its normal day-to-day function in healthy tissues. What the papers do show is that KLHL35 expression (how much the gene is "turned on") and KLHL35 DNA methylation (an epigenetic on/off-dimmer) repeatedly show up in studies of cancer biology and inflammatory cell-death pathways. That pattern suggests KLHL35 sits near the intersection of protein turnover (ubiquitin signaling), cell-cycle control, and stress/inflammation-related cell death programs. How your variant affects this: the variant you listed (rs756778027) is not described in these papers as changing KLHL35 protein structure or function, and the protein change is unknown. Because you are heterozygous (one

copy), even if the variant had some effect, the other copy often provides 'backup.' Based on the reviewed literature, this variant should currently be treated as a genetic finding with uncertain personal health impact—not as a diagnosis.

Evidence Summary: Across multiple cancers, higher KLHL35 expression is repeatedly associated with worse outcomes (colorectal cancer, colorectal liver metastasis signatures, head and neck cancer risk signatures) and KLHL35 shows up as a 'feature gene' in an Alzheimer's disease necroptosis-based subtype classifier. Separately, several studies report KLHL35 DNA methylation changes (in newborns exposed to maternal HBV, in offspring of older mothers, in abdominal aortic aneurysm blood cells, and in tumor tissues such as hepatocellular carcinoma and renal cell carcinoma). Important for you as a heterozygous carrier: none of the reviewed papers link rs756778027 specifically to disease risk, and none describe symptoms in heterozygous carriers. Most of the evidence is about gene expression/methylation differences in diseased tissues or bioinformatic prognostic models—not inherited variant effects. So, the actionable takeaway is to use this result as a prompt to focus on general, evidence-based prevention/early detection relevant to the diseases studied (especially colorectal cancer), rather than to expect a specific carrier syndrome.

4. Carrier Phenotype

Based on the papers you provided, being heterozygous for rs756778027 in KLHL35 does not come with a known, predictable 'carrier symptom' pattern. The research here mostly treats KLHL35 as a gene whose activity level (expression) or epigenetic state (methylation) changes in certain diseases—especially cancers—and as a contributor to statistical risk/prognosis models. So for you personally, the most honest interpretation is: this is a genetic finding of uncertain clinical significance in the carrier state, and it should not be assumed to raise or lower your disease risk without additional evidence (family history, personal history, and broader genetic context).

Can be symptomatic: Unknown/Rarely

Symptom frequency: Not documented in reviewed literature

5. Documented Triggers

HPV16 infection (productive/persistent epithelial infection context) (2019)

In organotypic epithelial models of productive HPV16 infection, KLHL35 was consistently upregulated across cervical, foreskin, and tonsil epithelium, alongside broad activation of cell-cycle and DNA-repair programs.

This suggests KLHL35 is part of the tissue response to HPV-driven cellular stress/proliferation—but the papers do not show that your inherited rs756778027 changes your response to HPV.

Prenatal HBV exposure / intrauterine HBV infection (2018)

A pilot human study reported differential KLHL35 methylation at birth in newborns exposed to maternal HBV infection. This is a 'trigger' in the sense that an infection exposure during pregnancy was associated with epigenetic changes in KLHL35, but it does not establish symptoms in carriers of rs756778027.

Older maternal age during pregnancy (epigenetic influence on offspring) (2016)

Two cohorts of newborns and a replication in adult women showed reduced methylation near KLHL35 with increasing maternal age. This is an exposure-associated epigenetic 'trigger' rather than a genetic variant trigger; no symptoms were attributed to this methylation change in the paper.

Smoking status (studied as a stratifier in AAA methylation study) (2015)

In an abdominal aortic aneurysm methylation study, groups were stratified by smoking and non-smoking, and KLHL35 was among regions differing with AAA status. The study design suggests smoking is an important co-factor to account for in inflammatory methylation patterns, but it does not prove smoking specifically interacts with rs756778027.

Cancer/tumor state (tumor microenvironment, metastasis context) (2025)

Multiple papers report that KLHL35 expression is higher in tumor tissues and associates with prognosis or metastasis-related features. In practical terms, this means KLHL35 is more of a 'tumor-state marker' in these studies than a lifestyle trigger. The reviewed literature does not identify day-to-day triggers (like fasting or exercise) that provoke symptoms in carriers.

6. Evidence-Based Recommendations

Lifestyle

COHORT

Treat this result as a 'prevention prompt': keep up with age-appropriate cancer screening and don't skip routine checkups.

CASE-CONTROL N=41

If you smoke, make quitting a high priority; if you don't, avoid starting and minimize secondhand smoke.

IN VITRO

Diet

Aim for a 'colon-friendly default': most meals built around fiber-rich plants (beans/lentils, vegetables, fruit, whole grains) and limit ultra-processed foods.

Prioritize infection prevention habits that are already known to reduce cancer risk: HPV vaccination (if eligible), safer sex, and keeping up with recommended cervical/HPV screening where applicable.

Exercise

Keep regular, moderate activity as your baseline (for example: brisk walking, cycling, swimming most days). If you're increasing intensity, ramp up gradually over weeks.

Supplements

None specifically recommended for KLHL35 rs756778027 based on reviewed papers : No KLHL35-targeted supplements are supported by the reviewed literature. If you take supplements, focus on correcting documented deficiencies (for example vitamin D, B12, iron) with your clinician.

Pharmaceuticals

Important: Consult your doctor before starting any medication.

None specific to KLHL35	(N/A)	No medications were studied or recommended in the reviewed papers for people with inherited KLHL35 variants. Any cancer-prevention or risk-reduction medication decisions should be based on standard risk factors and clinician guidance.	Side effects (mild): Not documented in reviewed literature.

Labs to Check

COHORT

Colorectal cancer screening (stool-based testing or colonoscopy per age/risk) : Multiple studies highlight KLHL35 as a colorectal/colon cancer biomarker or prognostic gene. That doesn't mean your variant causes CRC—but it does make colon health the most evidence-aligned area to be proactive about. *(Frequency: Follow standard guidelines based on age and personal/family history; not specified in reviewed literature.)*

CASE-CONTROL N=57

If you have chronic hepatitis risk factors: discuss HBV/HCV screening with your clinician	: KLHL35 methylation is described as a tumor biomarker in hepatocellular carcinoma and as epigenetically altered in HBV-related contexts. The papers don't support special testing purely because of rs756778027, but liver viral status is a major, modifiable driver of HCC risk.	*(Frequency: Not documented in reviewed literature.)*

Symptoms to Watch

COHORT | 3 CITES | URGENT

Persistent change in bowel habits, blood in stool, unexplained weight loss, or ongoing abdominal pain	These can be warning signs for colorectal disease. The KLHL35 literature is strongest in colorectal cancer prognosis/biomarker contexts, so it's reasonable to take gut symptoms seriously and not 'wait them out.'	*Action: Arrange a prompt medical evaluation rather than self-treating for weeks.*

COHORT | SOON

A new lump, persistent sore/throat symptoms, or unexplained bleeding in the head/neck area	KLHL35 is part of a pyroptosis-related prognostic signature in head and neck cancer; this doesn't mean you'll develop it, but it supports staying attentive to persistent symptoms.	*Action: If symptoms last >2–3 weeks, get checked.*

Things to Avoid

CASE-CONTROL | N=41 | Strictly Avoid

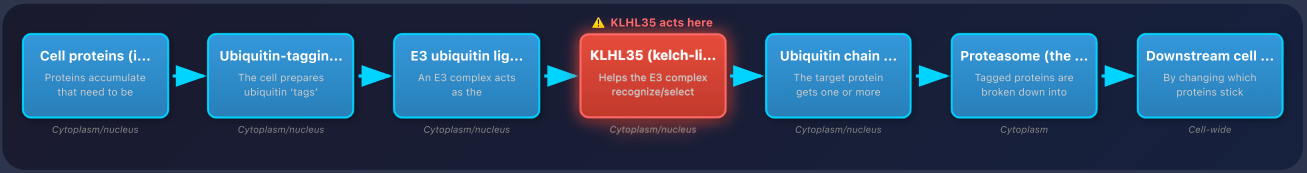
Smoking (including relapse after quitting)	(lifestyle)	Smoking is a major driver of inflammatory and vascular damage biology and was an explicit stratification factor in a KLHL35 methylation study in abdominal aortic aneurysm. While not a proven rs756778027 interaction, avoiding smoking is one of the highest-impact choices for the disease areas that overlap with this literature (vascular disease and cancer).

7. Key Biological Pathway ⓘ

🔬 Ubiquitin "tag-and-recycle" protein quality-control (KLHL adaptors)

Why this matters: This is the most consistent theme across the papers: KLHL35 repeatedly appears in studies framed around ubiquitin-related genes and cancer biology. If KLHL35 acts like other kelch-like proteins, its key role would be helping cells decide which proteins get 'tagged' for recycling—an upstream control point that can influence cell growth, stress responses, and inflammation.

Your cells constantly replace worn-out or unneeded proteins. The ubiquitin system is like putting a 'dispose/recycle' sticker on specific proteins so the cell's shredder (the proteasome) can break them down. KLHL35 is best thought of as a potential "selector arm" that helps choose which proteins get the sticker, although the exact targets for KLHL35 are not documented in the reviewed literature.



> **When this pathway is impaired:**
>
> If a KLHL-style selector is altered (by expression changes, methylation changes, or possibly damaging variants), the wrong proteins may be kept or removed. That can tilt cells toward abnormal growth (cancer-related behavior) or toward exaggerated stress/inflammation signaling. For rs756778027 specifically, this 'what goes wrong' model is plausible but not documented in the reviewed literature.

Other Related Pathways

No metabolic pathways associated with KLHL35 in KEGG. This gene may be involved in protein complexes or signaling rather than metabolic pathways.

8. Emergency Protocol

No KLHL35/rs756778027-specific emergency protocol is described in the reviewed literature. If you develop severe symptoms such as heavy bleeding, fainting, severe chest pain, sudden neurologic symptoms, or severe abdominal pain, follow standard emergency guidance and seek urgent care.

Warning Signs:

- Heavy bleeding
- Fainting or severe weakness
- Sudden severe headache or one-sided weakness
- Severe chest pain or shortness of breath

9. Protein Information

Protein Length	363 amino acids
Function	KLHL35 is a gene that produces a protein playing a vital role in keeping our cells healthy by helping to tag and recycle proteins. This process is key to making sure cells have just the right mix of p
Subcellular Location	Location not specified
Known Variants	0

10. Key References

Key References

1. COHORT **Analysis and experimental validation of necroptosis-related molecular classification, immune signature and feature genes in Alzheimer's disease.** (2024) PMID:38478169
   Supports variant mechanism understanding
2. COHORT 3 CITES **Construction of a Risk Model for Colon Cancer Prognosis Based on Ubiquitin-Related Genes.** (2023) PMID:37158531
   Supports variant mechanism understanding
3. COHORT 10 CITES **Multi-Omics Analysis of the Tumor Microenvironment in Liver Metastasis of Colorectal Cancer Identified FJX1 as a Novel Biomarker.** (2022) PMID:35928453
   Supports variant mechanism understanding
4. COHORT **Developing a pyroptosis-related gene signature to better predict the prognosis and immune status of patients with head and neck squamous cell carcinoma.** (2022) PMID:36685979
   Supports variant mechanism understanding
5. COHORT **Comprehensive analysis of KLHL35 expression and its prognostic value in cancer: implications for colorectal cancer diagnosis and therapy.** (2025)

PMID:41114922

Supports variant mechanism understanding

6. COHORT N=9 **Genome-wide methylation analysis identifies epigenetically inactivated candidate tumour suppressor genes in renal cell carcinoma.** (2011) PMID:21132003

   Supports variant mechanism understanding

7. IN VITRO **Tissue-Specific Gene Expression during Productive Human Papillomavirus 16 Infection of Cervical, Foreskin, and Tonsil Epithelium.** (2019) PMID:31189705

   Documents trigger: HPV16 infection (productive/persistent epithelial infection context)

8. CASE-CONTROL N=24 **Epigenome-wide study for the offspring exposed to maternal HBV infection during pregnancy, a pilot study.** (2018) PMID:29526602

   Documents trigger: Prenatal HBV exposure / intrauterine HBV infection

9. COHORT 69 CITES N=890 **Maternal Age at Delivery Is Associated with an Epigenetic Signature in Both Newborns and Adults** (2016) PMID:27383059

   Documents trigger: Older maternal age during pregnancy (epigenetic influence on offspring)

10. CASE-CONTROL N=41 **The potential role of DNA methylation in abdominal aortic aneurysms.** (2015) PMID:25993294

    Documents trigger: Smoking status (studied as a stratifier in AAA methylation study)

11. CASE-CONTROL N=57 **Genome-wide analysis of DNA methylation identifies novel cancer-related genes in hepatocellular carcinoma.** (2012) PMID:22457049

    Supports If you have chronic hepatitis risk factors: discuss HBV/HCV screening with your clinician monitoring

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ZNF425 — Full Report

1. Variant Information

Gene	ZNF425
Variant ID	rs769014744
Protein Change	p.C4B
Genotype	GACCT/G

ClinVar Classification	Not Applicable
Pathogenicity Score	14
Predicted Phenotype	Likely carrier

2. Associated Diseases

This is a **Loss-of-Function** variant with **High** impact. No specific disease associations in ClinVar.

3. Variant Mechanism

ZNF425 is a zinc-finger "gene switch" protein that can turn down (repress) the activity of other genes. Think of it like a dimmer knob that reduces how strongly certain growth-and-stress response programs run inside cells. In the one functional study provided, ZNF425 acted as a transcriptional repressor and, when over-expressed, it reduced signaling readouts from MAPK-linked transcription programs (SRE, AP-1, SRF), suggesting it can put the brakes on MAPK pathway output (Paper 2). How your specific variant affects this function is not directly shown in the reviewed literature. The rs769014744 genotype is listed, but the protein change and functional consequence of this specific allele were not reported in the two papers you provided. So, we cannot responsibly say whether it weakens or strengthens ZNF425 activity (Not documented in reviewed literature).

Evidence Summary: Two different kinds of evidence exist here: 1) Cell signaling biology: In lab experiments, extra ZNF425 in cells behaved like a brake on MAPK-linked transcription activity, consistent with a role as a transcriptional repressor (Paper 2). 2) Viral production screen: In a CRISPR knockout screen in HEK293T cells, ZNF425 was one of nine genes whose knockout increased lentiviral vector production, meaning ZNF425 normally limits some step(s) in lentivirus packaging/formation in that cell-factory context (Paper 1). Neither paper links rs769014744 to a human disease, symptoms, or clinical management in carriers. For a heterozygous carrier like you, the most accurate takeaway is: this is currently a research finding about gene regulation and viral production in cell lines, not a proven health-risk variant (Papers 1–2).

4. Carrier Phenotype

Based on the papers you provided, being heterozygous for rs769014744 in ZNF425 does not currently have a documented, predictable set of symptoms. The main evidence is from cell experiments showing what ZNF425 can do when over-expressed or knocked out in lab cell lines, not what naturally occurring carrier variants do in living people (Papers 1–2). So, for you as a carrier, the most practical message is: treat this as an "interesting research signal" about a gene involved in regulating cellular responses, rather than a diagnosis or a proven health risk. If you have symptoms you're worried about, they should be evaluated on their own merits rather than assumed to be caused by this variant (Not documented in reviewed literature).

Can be symptomatic: Unknown/Rarely

Symptom frequency: Unknown

5. Documented Triggers

No documented triggers available.

6. Evidence-Based Recommendations

Lifestyle

Use a "symptom-led" approach: if you notice a consistent pattern (e.g., certain stressors reliably worsen headaches, palpitations, rashes, or fatigue), track it and bring the log to your clinician.

Diet

None found during research

Exercise

None found during research

Supplements

None found during research

Pharmaceuticals

None found during research

Labs to Check

Routine preventive : Not documented in reviewed literature for

labs based on your age/medical history (e.g., lipids, A1c, CBC, CMP)	ZNF425. Included only as general health maintenance; it's not ZNF425-specific.	*(Frequency: As recommended by your primary care clinician)*

Symptoms to Watch

EMERGENCY

New or rapidly worsening neurologic symptoms (weakness on one side, trouble speaking, sudden vision loss)	Not documented in reviewed literature for ZNF425. These are general emergency warning signs unrelated to the provided papers, included for safety.	*Action: Seek emergency care immediately.*

Things to Avoid

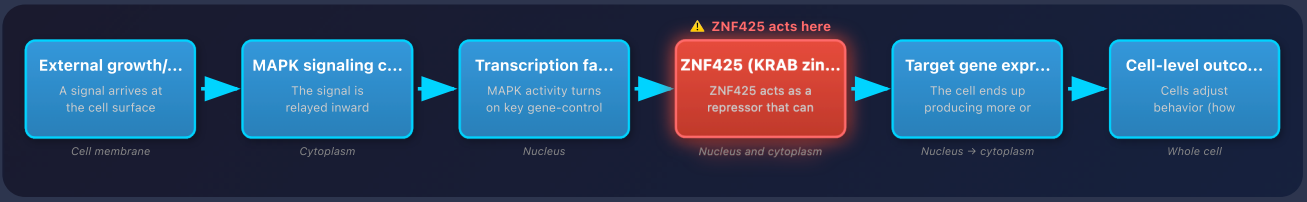
None found during research

7. Key Biological Pathway

MAPK "stress-to-gene-expression" signaling (AP-1/SRE/SRF output)

Why this matters: This is the central mechanism tied to ZNF425 in the reviewed papers: ZNF425 functions like a transcriptional brake that can reduce MAPK-linked gene-expression programs. Understanding this pathway helps you understand what ZNF425 influences (how cells respond to growth/stress signals), and it explains why changing ZNF425 activity could subtly shift cellular "response intensity." (Paper 2)

Your cells constantly receive signals—like growth cues or stress cues—and the MAPK pathway is one of the main wiring systems that turns those signals into gene activity changes. ZNF425 appears to act like a braking system on the final "gene expression" part of that response, dialing down certain MAPK-driven switches (Paper 2).



When this pathway is impaired:

Not documented in reviewed literature for rs769014744 or for heterozygous carriers. In theory, if ZNF425 activity were reduced, MAPK-linked transcription outputs could be less “braked,” and if increased, they could be more “braked”—but the reviewed papers do not connect this to symptoms or disease risk in people (Paper 2; Not documented for this variant).

Other Related Pathways

No metabolic pathways associated with ZNF425 in KEGG. This gene may be involved in protein complexes or signaling rather than metabolic pathways.

8. Emergency Protocol

Not documented in reviewed literature for ZNF425 rs769014744. Follow standard sick-day guidance from your clinician, especially if you have other medical conditions.

Warning Signs:

No warning signs documented.

9. Protein Information

Protein Length	752 amino acids
Function	ZNF425 normally produces a protein that acts like a regulator, helping to turn off certain genes during early development—especially in the heart. When the gene doesn't work as it should due to loss-o
Subcellular Location	Location not specified
Known Variants	0

10. Key References

Key References

1. IN VITRO **A novel human KRAB-related zinc finger gene ZNF425 inhibits mitogen-activated protein kinase signaling pathway.** (2011) PMID:21266108
   Supports variant mechanism understanding
2. IN VITRO 2 CITES **Engineering of HEK293T Cell Factory for Lentiviral Production by High-Throughput Selected Genes** (2024)
   PMID:a7617cdeffafed7a5df219f88591fb8c1da86215
   Supports variant mechanism understanding

FLG2 — Full Report

1. Variant Information

Gene	FLG2
Variant ID	rs556285121
Protein Change	p.L7A
Genotype	GTATT/G
ClinVar Classification	Not Applicable
Pathogenicity Score	14
Predicted Phenotype	Likely carrier

2. Associated Diseases

Peeling skin syndrome (FLG2-related)

Superficial skin peeling that can worsen with heat and friction; the skin's outer layer doesn't hold together as strongly as it should.

For carriers: Primarily documented in people with two nonworking copies (homozygous loss-of-function). Not documented in reviewed literature as a typical outcome for heterozygous carriers of rs556285121.

Eczema-prone skin barrier

Dry, itchy, inflamed skin that flares when the barrier is stressed; inflammatory signals can further weaken barrier proteins like FLG2.

For carriers: FLG2 is repeatedly downregulated in eczema lesions and inflammatory models; some FLG2 variants are associated with eczema risk in specific cohorts. For rs556285121 specifically, risk in heterozygous carriers is not documented in reviewed literature.

Allergy and asthma tendency in kids with eczema

In some children, early eczema can be followed by developing allergies and asthma; barrier genes may contribute to that pathway.

For carriers: Association in literature is with FLG2 rs12568784 (not rs556285121). Not documented for rs556285121 in reviewed literature.

Itchy blistering skin disease (modifier effect)

A rare inherited blistering disorder with very itchy thickened bumps and plaques; severity can vary a lot even within a family.

For carriers: One paper reports co-inheritance of an FLG2 mutation associated with greater intra-family variability in a COL7A1-caused disorder. This suggests FLG2 variants may modify severity in some genetic contexts; not a primary cause by itself in that study.

Hard-to-heal leg ulcers (in sickle cell disease)

Chronic skin ulcers on the legs that can be slow to heal and prone to infection in sickle cell disease.

For carriers: Association in literature is with a different FLG2 stop-gain variant (rs12568784) in sickle cell cohorts; not documented for rs556285121 in reviewed literature.

3. Variant Mechanism

FLG2 is a skin "barrier builder" protein made in the outer layers of the skin. Think of it like part of the mortar and glue that helps your skin's top layer (the stratum corneum) pack tightly, keep water in, keep irritants out, and support the skin's natural antimicrobial shield. Research shows that when FLG2 levels are reduced or missing, the outer skin layer forms abnormally: cell-to-cell adhesion is weaker, the skin surface pH rises, and the skin becomes more prone to barrier breakdown and irritation (e.g., under UVB or inflammatory cytokines). In your case, the exact protein change for rs556285121 is unknown from the provided literature, so we cannot say whether this specific heterozygous variant reduces FLG2 function. However, it sits in a gene where reduced expression/function is repeatedly linked to barrier vulnerability and inflammation-related downregulation in eczema/psoriasis models.

Evidence Summary: Overall, the papers support a clear theme: FLG2 helps build a resilient, well-sealed outer skin layer and contributes to antimicrobial defense. When FLG2 is deficient (especially with loss-of-function variants in two copies), people can develop peeling skin syndromes and heat/mechanical-stress–exacerbated peeling. In inflammatory skin diseases like atopic dermatitis, FLG2 expression is commonly reduced in lesions, and cytokines such as IL-4/IL-13/IL-22 and TNF-α/IL-17A/IL-22 can further push FLG2 down, worsening barrier integrity. For heterozygous carriers of a specific FLG2 variant like rs556285121, the reviewed literature does not document a consistent, stand-alone carrier syndrome; instead, FLG2 variation appears to act more like a modifier—potentially influencing severity or variability when other strong skin disease genes are present (e.g., COL7A1 in DEB-Pr) or within multifactorial eczema risk contexts.

4. Carrier Phenotype

Because you're heterozygous (one copy) for rs556285121, the big question is whether a single altered copy meaningfully lowers FLG2 function. In the papers reviewed, clear, severe FLG2 diseases (like peeling skin syndrome) were reported when people had two nonworking copies (homozygous loss-of-function), not in single-copy carriers (PMID: 29758285; PMID: 28884927). For carriers, the best-supported idea is that FLG2 variation can act as a 'modifier'—it may nudge skin barrier resilience up or down, especially when combined with other risk factors (other genes, inflammation, irritants, dry climate). One case series in a different genetic disease (DEB-Pr) noted that co-inheriting an FLG2 mutation tracked with intra-family variability (PMID: 34543471). That means: you may be completely asymptomatic, but if you do get eczema-prone or sensitive skin, your barrier may have slightly less reserve under stressors like heat, friction, harsh soaps, UVB, and inflammatory flares.

Can be symptomatic: Unknown/Rarely

Symptom frequency: Unknown

5. Documented Triggers

Heat exposure / temperature elevation (2018)

Heat can worsen the consequences of low FLG2 because higher temperatures further weaken keratinocyte cell-to-cell adhesion when FLG2 is down, matching clinical worsening of peeling with heat.

Mechanical stress / friction (2018)

When the ‘glue’ between outer skin cells is weaker (as seen with FLG2 deficiency), rubbing and mechanical stress make the top layer detach more easily.

UVB (sunburn-type ultraviolet exposure) (2015)

FLG2 downregulation in reconstructed epidermis increased sensitivity to UVB, consistent with a barrier that can’t buffer environmental stress as well.

Type-2 inflammation (IL-4 and IL-13) (2025)

IL-4 and IL-13 directly downregulate FLG2 and other barrier proteins in ex vivo human skin and 3D atopic dermatitis models, which can worsen dryness/itch and barrier leakiness during eczema flares.

IL-22-driven inflammation (Th22) (2025)

IL-22 reduces FLG2 and disrupts barrier integrity in ex vivo human skin and 3D psoriatic models, meaning some inflammatory patterns can specifically suppress barrier building blocks.

TNF-α and IL-17A inflammation (psoriasis-like cytokines) (2024)

In a 3D psoriatic skin model, TNF-α and IL-17A reduced FLG2 expression, suggesting inflammatory flares can push FLG2 lower and impair barrier structure.

6. Evidence-Based Recommendations

Lifestyle

REVIEW

Make ‘barrier care’ a daily habit: short lukewarm showers, gentle fragrance-free cleanser only where needed, and moisturize within 3 minutes of drying off.

REVIEW

Use a humidifier in the bedroom during dry seasons (aim for comfortable, non-musty humidity).

CASE REPORT

Plan for heat/friction days: choose breathable fabrics, reduce rubbing (seams, tight socks), and moisturize before activities that cause chafing.

REVIEW

Treat stress like skin care: build a simple downshift routine (10 minutes/day of walking, breathing, or journaling) and protect sleep.

Diet

If you notice eczema/itch flares, keep a simple 2-week ‘skin diary’ (foods, new products, stress, weather) before eliminating foods.

Exercise

CASE REPORT

Stay active, but protect your skin barrier during workouts: shower soon after sweating, use a gentle cleanser, and re-moisturize; choose clothing that minimizes rubbing.

Supplements

None found during research

Pharmaceuticals

Important: Consult your doctor before starting any medication.

Dupilumab (IL-4Rα antagonist (blocks IL-4/IL-13 signaling)) — If you ever develop moderate-to-severe atopic dermatitis that isn't controlled with topical therapy, ask a dermatologist whether a type-2 targeted biologic like dupilumab makes sense for you. — Side effects (moderate): Not documented in reviewed literature (side effects were not described in the provided abstract).

ANIMAL N=16

Oclacitinib (JAK inhibitor (veterinary use)) — Not applicable for human treatment; included here only because it illustrates that reducing inflammation/trauma can increase FLG2 expression in atopic skin in an animal model. — Side effects (moderate): Not documented in reviewed literature (veterinary abstract did not detail adverse effects).

Labs to Check

REVIEW

Atopic dermatitis assessment by clinician (severity scoring + trigger review) — : Because FLG2 is a barrier gene that is downregulated during AD inflammation, tracking eczema severity and triggers helps you intervene early before the barrier-inflammation cycle escalates. — *(Frequency: If symptoms develop: at diagnosis, then every 3–12 months depending on control)*

N=40

Patch testing for contact allergy (e.g., nickel) if recurrent dermatitis — : Human sensitizer models show allergens can drive inflammation and downregulate FLG2 and other barrier genes. If you keep flaring despite good barrier care, contact allergy is worth checking. — *(Frequency: As needed (persistent/recurrent dermatitis))*

Symptoms to Watch

SOON

Things to Avoid

CASE REPORT Caution

Persistent itch with dry, rough, or inflamed patches (especially in flexures, hands, or legs)

Itch and dryness can be early signs that the barrier is leaking and inflammation is suppressing barrier proteins like FLG2, which can perpetuate flares.

Action: Step up barrier care for 1–2 weeks (gentle cleansing + frequent moisturizing) and consider seeing a dermatologist if it's not improving.

CASE REPORT SOON

Skin peeling that worsens with heat or friction

FLG2 deficiency can weaken cell-to-cell adhesion in the outer skin, making peeling more likely under heat/mechanical stress.

Action: Reduce heat exposure/friction, moisturize, and seek dermatology evaluation if persistent or widespread.

IN VITRO ROUTINE

Stinging/burning with skincare products (especially acids)

Lactic acid exposure in models reduced barrier resistance and downregulated FLG2 while activating stress/itch pathways, which mirrors 'sensitive skin' reactions.

Action: Stop the triggering product, simplify to bland moisturizer and gentle cleanser, and reintroduce actives slowly (or avoid if repeat).

IN VITRO 30 CITES URGENT

Repeated skin infections or slow-healing irritated areas

FLG2 fragments have antimicrobial activity (especially against Pseudomonas), and a weaker barrier can allow microbes to gain a foothold.

Action: Seek medical care for signs of infection (spreading redness, warmth, pus, fever).

Overheating and prolonged hot baths/saunas if they trigger peeling or flares (lifestyle)

Heat can aggravate cell-to-cell adhesion problems when FLG2 is deficient, and can act as a barrier 'stress test.'

CASE REPORT Caution

High-friction clothing or repetitive rubbing on the same skin areas (lifestyle)

Mechanical stress worsened peeling in FLG2 deficiency; reducing friction protects the outer layer's adhesion system.

IN VITRO 63 CITES Avoid

Unprotected UVB exposure (sunburn) (lifestyle)

FLG2 downregulation increased UVB sensitivity in reconstructed epidermis, consistent with reduced buffering against UV stress.

Caution

Not documented in reviewed literature (diet)

No diet items were specifically identified as FLG2-related triggers in the provided papers.

REVIEW Avoid

Harsh/basic (high-pH) soaps and strong surfactants (other)

High-pH cleansing is an AD trigger and FLG2 deficiency is linked with higher surface pH; together this can disrupt lipid processing and promote inflammation.

IN VITRO Caution

At-home high-strength lactic acid products if they cause stinging/itch (other)

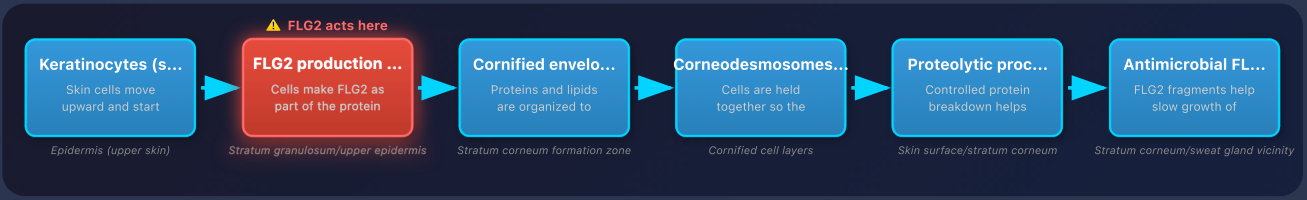
Lactic acid reduced barrier resistance and downregulated FLG2 in reconstructed epidermis while activating itch/stress pathways.

7. Key Biological Pathway

Skin barrier cornification & corneodesmosome adhesion (the ‘brick-and-mortar’ barrier)

Why this matters: This is the central mechanism that connects FLG2 to real-world symptoms: dryness, irritation, eczema-like inflammation, sensitivity to soaps/chemicals, and—in severe deficiency—peeling. FLG2 supports how skin cells mature into a tough outer layer and helps maintain cell-to-cell adhesion and antimicrobial defense; when this process is disrupted, the barrier leaks water and lets irritants/microbes in, fueling inflammation that can further suppress FLG2.

Your outer skin layer is like a brick wall: the cells are the bricks, and proteins/lipids are the mortar and glue. FLG2 helps the ‘mortar/glue’ system form correctly and stay tightly stuck together. When FLG2 is low, the wall gets leaky and fragile, especially under stress like heat, friction, UVB, harsh soaps, or inflammation.



When this pathway is impaired:

When FLG2 is deficient or pushed down by inflammation, the stratum corneum can become abnormally formed, less well-hydrated, and higher in pH; cell-to-cell adhesion can weaken and the skin may become more sensitive to UVB and irritants. Microbes and allergens can penetrate more easily, which can trigger type-2 inflammation (IL-4/IL-13) and IL-22 pathways that further reduce key barrier proteins (including FLG2), creating a ‘leaky barrier → inflammation → leakier barrier’ cycle.

Other Related Pathways

Cornified envelope formation

KEGG: hsa04382

View Details →

Associated Conditions (KEGG)

- H00737 Peeling skin syndrome
- 09150 Organismal Systems
- 09158 Development and regeneration
- 04382 Cornified envelope formation

- 388698 (FLG2)

8. Emergency Protocol

This variant is not associated with a systemic metabolic 'illness emergency' protocol in the reviewed literature. If you have severe widespread skin peeling, rapidly spreading redness, fever, or signs of skin infection, seek urgent medical care because barrier breakdown can increase infection risk.

Warning Signs:

- Rapidly spreading redness/warmth
- Pus or increasing pain
- Fever with skin symptoms
- Large areas of peeling after heat/friction

9. Protein Information

Protein Length	75 amino acids
Function	FLG2 is a gene that produces filaggrin-2, an important protein for healthy skin. It helps form the skin's protective outer layer, keeps the skin moisturized, and defends against environmental germs. W
Subcellular Location	Location not specified
Known Variants	0

10. Key References

Key References

1. REVIEW **Filaggrinopathies-FLG/FLG2: Diagnostic Complexities and Immunotherapy.** (2025) PMID:39927906
   Supports variant mechanism understanding
2. IN VITRO 63 CITES **In a three-dimensional reconstructed human epidermis filaggrin-2 is essential for proper cornification** (2015) PMID:25695608
   Supports variant mechanism understanding
3. CASE REPORT **Filaggrin 2 Deficiency Results in Abnormal Cell-Cell Adhesion in the Cornified Cell Layers and Causes Peeling Skin Syndrome Type A.** (2018) PMID:29758285
   Supports variant mechanism understanding
4. **Distinct Roles of IL-4, IL-13, and IL-22 in Human Skin Barrier Dysfunction and Atopic Dermatitis.** (2025) PMID:40985485
   Supports variant mechanism understanding
5. IN VITRO **Effect of tumour necrotic factor-α, interleukin-17 and interleukin-22 on the expression of filaggerin-2 and hornerin: Analysis of a three-dimensional psoriatic skin model.** (2024) PMID:39624730
   Supports variant mechanism understanding
6. IN VITRO 30 CITES **Skin-Derived C-Terminal Filaggrin-2 Fragments Are Pseudomonas aeruginosa-Directed Antimicrobials Targeting Bacterial Replication.** (2015) PMID:26371476
   Supports variant mechanism understanding
7. REVIEW **Could cellular and signaling abnormalities converge to provoke atopic dermatitis?** (2020) PMID:33048449
   Documents trigger: Harsh soaps/surfactants and basic (high-pH) cleansing
8. IN VITRO **Transcriptional profiling of lactic acid treated reconstructed human epidermis reveals pathways underlying stinging and itch.** (2019) PMID:30851411
   Documents trigger: Lactic acid (5%) topical exposure (some cosmetics/peels)
9. N=40 **Delayed type hypersensitivity reactions to various allergens may differently model inflammatory skin diseases.** (2023) PMID:36178084
   Documents trigger: Allergen/sensitizer exposure (e.g., DPCP, nickel, dust mite, PPD)
10. CASE REPORT **Peeling skin syndrome associated with novel variant in FLG2 gene.** (2017) PMID:28884927
    Supports carrier phenotype information
11. CASE SERIES N=7 **Dystrophic epidermolysis bullosa pruriginosa: a new case series of a rare phenotype unveils skewed Th2 immunity.** (2022) PMID:34543471
    Supports carrier phenotype information

12. ANIMAL N=16 **Evaluation of filaggrin 2 expression in dogs with atopic dermatitis before and after oclacitinib maleate administration.** (2025) PMID:40042058

Supports Oclacitinib pharmaceutical recommendation

ZNF492 — Full Report

1. Variant Information

Gene	ZNF492
Variant ID	rs370410008
Protein Change	p.T1B
Genotype	G|G
ClinVar Classification	Not Applicable
Pathogenicity Score	13
Predicted Phenotype	Likely affected

2. Associated Diseases

Kidney cancer progression marker (ZNF492 methylation)

In kidney cancer tumor tissue, higher DNA methylation of ZNF492 is linked to faster disease progression and poorer outcomes; it's being studied as a prognostic marker.

For carriers: This is about methylation changes in tumor tissue, not inherited rs370410008 genotype. Not documented in reviewed literature that carriers have increased risk or that this SNP drives methylation.

Liver cancer immunotherapy response signature

ZNF492 was one of 16 genes used in a combined score that correlated with immune cell activity and predicted which liver cancer patients might respond better to immunotherapy.

For carriers: This finding relates to tumor gene expression patterns in people who already have liver cancer. Not documented in reviewed literature that rs370410008 affects immunotherapy response or liver cancer risk.

Triple X syndrome methylation differences (ZNF492 region)

In Triple X syndrome, certain regions near ZNF492 showed different DNA methylation patterns in blood compared with controls, though overall expression patterns were broadly comparable.

For carriers: This is driven by sex chromosome dosage (47,XXX), not by rs370410008 status. Not documented in reviewed literature that this variant causes or modifies Triple X syndrome features.

Retinal gene regulation role (cell model)

In a retinal cell model, ZNF492 binds the RPE65 gene's promoter and modestly increases its activity; reducing ZNF492 lowers promoter activity.

For carriers: This is mechanistic cell-model evidence. Not documented in reviewed literature that rs370410008 affects vision or retinal health in carriers or homozygotes.

3. Variant Mechanism

ZNF492 is a zinc-finger "gene switch" protein—a transcription factor that can bind DNA near certain genes and nudge their activity up or down. Think of it like a dimmer knob that helps set the brightness of specific genes in certain tissues. In the reviewed literature, ZNF492 was shown to bind the promoter region (the on/off control panel) of the RPE65 gene in retinal pigment epithelium (RPE) cells and modestly increase its activity; when ZNF492 was reduced with siRNA, RPE65 promoter activity dropped, supporting a real regulatory role (Paper 4: "Identification of a KRAB-zinc finger protein binding to the Rpe65 gene promoter."). ZNF492 also appears in cancer research as a gene whose DNA methylation (a chemical "lock" on DNA that often reduces gene expression) is associated with tumor progression in clear cell renal cell carcinoma, and as part of a gene-expression model linked to liver cancer immunotherapy response (Papers 3 and 1). How your specific variant (rs370410008, G|G) affects ZNF492 function is not documented in the reviewed literature. The papers discuss ZNF492 expression and methylation patterns, but they do not study this SNP's impact on protein function, gene expression, or health outcomes.

Evidence Summary: What we can say from these papers: ZNF492 is involved in regulating other genes (especially shown in retinal cells), and changes in its methylation/expression show up as markers in certain cancers. What we cannot say from these papers: that rs370410008 causes disease, changes your cancer risk, or alters immune therapy response. This specific variant is not analyzed in these studies, so any direct health guidance tied specifically to rs370410008 would be speculative (Not documented in reviewed literature).

4. Carrier Phenotype

Based on the reviewed papers, there is no documented symptom pattern for people who carry rs370410008 in ZNF492—either heterozygous or homozygous. The studies focus on ZNF492's role as a transcription factor in a retinal cell model (Paper 4) and as a methylation/expression marker in cancers and chromosomal conditions (Papers 1–3), but they do not link this specific variant to any clinical symptoms. So, if you were heterozygous (one copy), the best-supported interpretation from these papers is: we don't currently know of a specific health effect or trigger pattern attributable to being a carrier (Not documented in reviewed literature).

Can be symptomatic: Unknown/Rarely

Symptom frequency: Unknown

5. Documented Triggers

No documented triggers available.

6. Evidence-Based Recommendations

Lifestyle

COHORT

Treat this result as "research context," not a diagnosis—focus on the health basics you can control (sleep, not smoking, alcohol moderation, sun protection, routine care).

COHORT N=12

If you have (or ever develop) a cancer diagnosis, ask your oncology team whether tumor DNA methylation or gene-expression profiling is being used to guide prognosis or treatment.

Diet

None found during research

Exercise

None found during research

Supplements

None found during research

Pharmaceuticals

None found during research

Labs to Check

COHORT N=12

Standard age-appropriate cancer screening (per general population guidelines)	: The papers connect ZNF492 to cancer biology as a marker (methylation/expression) rather than an inherited risk variant. Nothing in the reviewed literature supports extra screening solely because of rs370410008; staying current with routine screening is a practical way to be proactive without over-medicalizing this finding.	*(Frequency: Follow standard national guidelines for your age/sex and personal/family history)*

Symptoms to Watch

None found during research

Things to Avoid

None found during research

7. Key Biological Pathway ⓘ

Gene regulation via promoter binding (ZNF492 as a transcription “dimmer switch”)

Why this matters: Across the reviewed papers, the most direct, experimentally tested role for ZNF492 is as a DNA-binding transcription factor that attaches to a gene’s promoter and adjusts how much that gene is turned on—demonstrated for the RPE65 promoter in retinal cells (Paper 4). This is the clearest mechanism to understand because it explains how changes in ZNF492 activity (from genetics, epigenetics like methylation, or cellular context) could ripple out to affect downstream genes.

Your cells run on “instruction manuals” (genes), and they use “switches” (promoters) to decide which manuals to read more or less. ZNF492 is one of the proteins that can physically sit on a promoter and tweak how strongly a gene is read. If ZNF492’s ability to bind DNA or recruit helper proteins changes, the output of certain genes can shift—like dimming or brightening a light—potentially affecting specific tissues where those genes matter (Paper 4).

When this pathway is impaired:

Not documented in reviewed literature for rs370410008. In general, if ZNF492 binding or regulatory activity were reduced, some target genes could be under-expressed; if increased, they could be over-expressed. Paper 4 shows that lowering ZNF492 in RPE cells lowers RPE65 promoter activity, illustrating the direction of effect in that model.

Other Related Pathways

No metabolic pathways associated with ZNF492 in KEGG. This gene may be involved in protein complexes or signaling rather than metabolic pathways.

8. Emergency Protocol

No variant-specific emergency or illness protocol is documented in the reviewed literature for rs370410008 in ZNF492. If you develop severe symptoms during illness (confusion, chest pain, severe shortness of breath, uncontrolled vomiting, fainting), follow standard emergency guidance and seek urgent care.

Warning Signs:

- Severe chest pain
- Trouble breathing
- Fainting
- New confusion
- Severe dehydration

9. Protein Information

Protein Length	531 amino acids

Function	ZNF492 is a gene that provides instructions for making a protein which helps control other genes in our cells. By binding to DNA, this protein plays a role in regulating cellular activities. When chan
Subcellular Location	Location not specified
Known Variants	0

10. Key References

Key References

1. IN VITRO **Identification of a KRAB-zinc finger protein binding to the Rpe65 gene promoter.** (2006) PMID:16714237
   Supports variant mechanism understanding
2. COHORT N=12 **ZNF492 and GPR149 methylation patterns as prognostic markers for clear cell renal cell carcinoma: Array-based DNA methylation profiling.** (2019) PMID:31115548
   Supports variant mechanism understanding
3. COHORT **Research into the characteristic molecules significantly affecting liver cancer immunotherapy.** (2023) PMID:36860864
   Supports variant mechanism understanding
4. CASE-CONTROL N=21 **Epigenetic and transcriptomic consequences of excess X-chromosome material in 47,XXX syndrome-A comparison with Turner syndrome and 46,XX females.** (2020) PMID:32489015
   Supports variant mechanism understanding

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