SelfDecode

WHOLE GENOME SEQUENCING ANALYSIS

Rare Variants Report

36 TOTAL RARE VARIANTS FOUND

Report Date: 16 June 2026

CLIENT	AGE	SEX	HEIGHT	WEIGHT
Joe GxG-WGS	37	Male	5ft 8" / 173cm	170lb / 77.1kg

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PROVIDED BY

This report is intended for informational and educational purposes only and is not a diagnostic test. All findings should be reviewed with a qualified healthcare provider. Genetic counseling is strongly recommended to support interpretation and clinical decision-making.

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How This Works

A short guide to reading your Rare Variants report — what we look for, how we group it, and what each finding does (and doesn't) mean.

WHAT THIS REPORT DOES

This report analyzes your whole genome sequence to identify rare genetic variants, which are places where your DNA differs from the majority of the population. The most informative findings are then organized into three sections:

SECTION 1

DISEASE-ASSOCIATED VARIANTS

Variants in genes known to cause specific diseases, mostly inherited in a Mendelian pattern (passed down through families in predictable ways). We focus on variants that have been classified as **pathogenic** or **likely pathogenic** in databases such as ClinVar and ClinGen, public databases curated by clinical and research laboratories worldwide. Most of these are associated with rare diseases.

SECTION 2

RISK-ASSOCIATED VARIANTS

Variants that don't cause disease on their own, but meaningfully shift the risk up or down, for common, complex conditions like cardiovascular disease or type 2 diabetes. These conditions are **polygenic**, meaning they emerge from the combined effect of many genes and lifestyle and environmental factors. However, the variants flagged here have unusually large individual effects compared to typical risk variants found in polygenic risk scores (PRS).

SECTION 3

LOSS-OF-FUNCTION VARIANTS

Variants that likely break one copy of a gene, but where no clear disease has been linked to that variant in the scientific literature. These may point to biological pathways that are operating below typical capacity (**Impactful**), which may warrant monitoring, lifestyle adjustments, or a conversation with your doctor. However, for most of these variants, a single intact copy is fully sufficient, and these variants likely have no significant impact on your health (**Informative**).

GENETICS CONCEPTS THAT MATTER FOR READING THIS REPORT

1 **Most disease-causing variants are recessive.**

You inherit two copies of nearly every gene — one from each biological parent. For recessive conditions, both copies need to be affected before symptoms appear. If you carry just one affected copy, you are a **carrier**: typically healthy yourself, but able to pass the variant to your children. This is why a "pathogenic" variant in your report often does **NOT** mean you will develop the associated disease.

2 **Even dominant variants don't always cause disease — this is called *penetrance*.**

Some variants are dominant, meaning a single affected copy is enough to potentially cause the condition. But genetics is rarely all-or-nothing. **Penetrance** describes the probability that someone carrying a variant will actually develop the associated trait or disease. A variant with 60% penetrance means roughly 6 out of 10 carriers will be affected — and 4 out of 10 will not, despite having the same variant. Penetrance varies enormously: some variants are nearly fully penetrant; others affect only a small fraction of carriers. **Expressivity** — how severely the condition manifests — also varies between people, even within the same family. This means people with the same variant can have different symptoms and different symptom severity.

3 **This means a variant flagged here is a statistical signal, not a verdict.**

Your overall risk depends on the specific variant, the rest of your genetic background, environmental factors, lifestyle, and often plain chance.

HOW TO READ YOUR RESULTS

SECTION 1 A finding in Section 1 does **not** mean you have, or will develop, the associated disease. Confirmation requires clinical evaluation, often including a second test from a certified diagnostic lab.

SECTION 2 A finding in Section 2 represents a **shift in probability**, not a prediction. Most complex diseases remain heavily influenced by modifiable factors.

SECTION 3 A finding in Section 3 is **exploratory**. It identifies genes worth being aware of, not problems to be fixed.

NO FINDINGS The **absence** of a finding does not mean you are free of genetic risk. This report only flags variants we can confidently interpret given current scientific knowledge — which is incomplete and evolving.

IMPORTANT TO KNOW

Keep the following in mind as you read your results:

⚠ **This is not a diagnostic test.**
This report is intended for informational and educational purposes. It is not a substitute for professional medical advice, diagnosis, or treatment. Do not start, stop, or change any medical treatment based on this report alone.

⚠ **Talk to a qualified professional.**
If any finding concerns you, or if you are considering acting on the information here, please consult a licensed physician or, ideally, a board-certified genetic counselor. Genetic counselors are specifically trained to help interpret results like these in the context of your personal and family history.

⚠ **Clinical confirmation is required for medical decisions.**
Variants identified through whole genome sequencing should be confirmed by a clinically certified laboratory (e.g., CLIA-certified in the United States, or equivalent) before being used to guide medical care.

⚠ **Knowledge changes.**
Variant classifications can and do change as more data accumulates. A variant considered pathogenic today may be reclassified tomorrow, and vice versa. We recommend re-reviewing your report periodically.

⚠ **Family implications.**
Your genetic information is partially shared with your biological relatives. Findings in this report may have implications for parents, siblings, and children. Consider this before sharing results.

Your Results at a Glance

What should I care about? Here's your personalized summary of all rare variants found.

4

DISEASE-ASSOCIATED VARIANTS

These variants are linked to known diseases. Status indicates if you're a carrier or affected.

0

RISK-ASSOCIATED VARIANTS

These variants increase or decrease your risk for specific conditions.

32

LOSS-OF-FUNCTION VARIANTS

These variants have mutations that affect gene function. Status indicates if your findings are impactful or informative.

Your Genetic Story: Your results cover 36 variants across 35 genes, and the most reassuring thing to know upfront is that the vast majority are single altered copies of recessive genes. Your second, working copy in each case is doing its job without any impact on your daily health. Your genome is, on balance, a resilient one.

Three findings deserve genuine attention. Your SHOX deletion confirms Leri-Weill Dyschondrosteosis. At 36 your height is set, so the focus now is your wrists and forearms: Madelung deformity and stiffness can still develop or worsen in adulthood. Your ABCA7 variant is not a certainty, but it is meaningful: large studies link this class of loss-of-function variant to roughly double the population-level lifetime risk of late-onset Alzheimer's disease, and a preliminary signal from your ITIH2 variant adds modest weight in the same direction. Your 30s are the right time to establish a cognitive baseline. Your CPT2 S113L variant is the one finding where a single altered copy can matter day to day: the enzyme is heat-sensitive, and published case series document muscle pain and, rarely, dangerous muscle breakdown in some single-copy individuals during intense exercise, fasting, or fever. Simple habits make this manageable.

The final theme is family planning. You carry single altered copies of CPT2, NEB, DUOXA2, TRIM32, and FLG2. None affect your health now, but together they make partner carrier testing an important conversation before you plan a family. A genetic counsellor can turn this long list into a focused, efficient plan.

GENE	VARIANT	PROTEIN	GENOTYPE	CONDITION / FUNCTION	STATUS
DISEASE-ASSOCIATED					
SHOX	X-647522-648178-G-<DEL>-DEL	NP_000442.1:5/5	N/<DEL>	Leri-Weill Dyschondrosteosis	LIKELY AFFECTED
CPT2	rs74315294	NP_000089.1:p.Ser113Leu	C/T	Carnitine Palmitoyltransferase Deficiency	LIKELY CARRIER
DUOXA2	rs201506037	Altered protein assembly	T/C	Thyroid Dyshormonogenesis	LIKELY CARRIER
NEB	2-151598566-151609129-T-<DEL>-DEL	NP_001157980.2:82-89/182	N/<DEL>	Nemaline Myopathy	LIKELY CARRIER
LOSS-OF-FUNCTION					
ABCA7	rs201060968	NP_061985.2:p.Trp1214Ter	G/A	Brain amyloid clearance	IMPACTFUL
ITIH2	rs151229507	Altered protein assembly	G/C	Cell matrix stability	IMPACTFUL
OR2T11	1-248576305-248647941-C-<DEL>-CNV	NP_001001964.1	N/<DEL>	Smell detection	IMPACTFUL
SLC22A14	rs138257211	NP_001306962.1:p.Leu238SerfsTer25	ATTTG/A	Sperm energy transport	IMPACTFUL

GENE	VARIANT	PROTEIN	GENOTYPE	CONDITION / FUNCTION	STATUS
TLR10	rs187892716	NP_112218.2:p.Ser245Ter	G/T	Immune inflammation control	IMPACTFUL
TRIM32	rs199664043	NP_036342.2:p.Arg613Ter	C/T	Protein recycling	IMPACTFUL
AGAP6	rs575835505	NP_001071133.2:p.Arg70GlyfsTer53	AC/A	Cell cargo transport	INFORMATIVE
ANKRD36	rs141447363	NP_001341516.1:p.Lys5SerfsTer29	GC/G	Sodium balance	INFORMATIVE
CCT8L2	rs139948519	NP_055221.1:p.Trp365Ter	C/T	Protein folding	INFORMATIVE
DHDH	rs10423255	NP_055290.1:p.Gln233Ter	C/T	Chemical detoxification	INFORMATIVE
FLG2	rs556285121	NP_001014364.1:p.Gln1034ProfsTer192	GTATT/G	Skin barrier protection	INFORMATIVE
GSDMC	rs16904150	Altered protein assembly	C/T	Cell death signaling	INFORMATIVE
GSTA4	rs749259552	NP_001503.1:p.Thr185SerfsTer5	CTG/C	Cell detoxification	INFORMATIVE
KLHL35	rs756778027	NP_001034637.2:p.Ser68AlafsTer121	TCGGGCCGCCCGGCCGCGAACAAGCTG/T	Protein recycling	INFORMATIVE
MFSD4B	rs117505745	NP_699200.2:p.Leu182Ter	T|A	Nutrient transport	INFORMATIVE
MST1	rs142690032	NP_066278.3:p.Arg651Ter	G/A	Immune gut signaling	INFORMATIVE
MYCT1	rs3841162	NP_079383.2:p.Asp22GlufsTer34	GAGAT/G	Cell growth control	INFORMATIVE
NOXO1	rs200352693	NP_751907.1:p.His193ProfsTer38	GT/G	Immune ROS signaling	INFORMATIVE
OR2D3	rs59264610	NP_001004684.1:p.Leu121PhefsTer13	TC/T	Smell detection	INFORMATIVE
OR2T35	1-248576305-248647941-C-<DEL>-CNV	NP_001001827.1	N/<DEL>	Smell detection	INFORMATIVE
OR5B3	rs200799158	NP_001005469.1:p.Phe31SerfsTer16	AG/A	Smell detection	INFORMATIVE
PCSK4	rs200944148	NP_060043.2:p.Gln141Ter	G/A	Reproductive function	INFORMATIVE
POTEA	rs557897303	XP_024302914.1:p.Asp430IlefsTer43	AG/A	Cancer/testis signaling	INFORMATIVE
SMIM22	rs778473760	NP_001240723.1:p.Gly42AlafsTer30	AG|A	Lipid droplet regulation	INFORMATIVE
SMIM22	rs745437189	NP_001240723.1:p.Thr43SerfsTer27	ACCGTGCT|A	Lipid droplet regulation	INFORMATIVE
SPATA31C1	9-87915586-87919008-C-<DEL>-DEL	NP_001138596.1:1/4	N/<DEL>	Spermatogenesis	INFORMATIVE
TAS2R19	rs777991764	NP_795369.1:p.Arg210AlafsTer4	G/GC	Bitter taste perception	INFORMATIVE

GENE	VARIANT	PROTEIN	GENOTYPE	CONDITION / FUNCTION	STATUS
TMEM59	rs200790405	Altered protein assembly	C/T	Cellular self-cleaning	INFORMATIVE
TPSB2	rs782257892	NP_077078.5:p.Met153AspfsTer14	C/CG	Immune signaling	INFORMATIVE
TPTE	21-10511076-10623497-A-<DEL>-CNV	NP_954870.3	N/<DEL>	Cell signal tuning	INFORMATIVE
ZNF425	rs769014744	NP_001001661.1:p.Lys518ThrfsTer51	GACCT/G	Gene activity control	INFORMATIVE
ZNF440	rs200705543	NP_689570.2:p.Arg412Ter	C/T	Gene regulation	INFORMATIVE

What This Means For You

Consolidated recommendations across all your rare variants.

Know Your CPT2 Triggers and Act Fast if Muscles Break Down

Your CPT2 S113L enzyme is heat-sensitive, so prolonged exercise, fasting, or fever can push muscles into an energy shortfall. Eat carbohydrates before and during sustained exercise, and stay well-fed during illness. If muscle pain feels out of proportion to effort, stop and eat. Dark or cola-coloured urine after exercise or illness means go to an emergency department the same day and mention CPT2. Tell any anaesthetist about this variant before surgery.

CPT2

Protect Your Wrists and Document Your SHOX Diagnosis

Your SHOX deletion confirms Leri-Weill Dyschondrosteosis. Wrist stiffness and Madelung deformity can develop or worsen even in adulthood. See an orthopaedic physician if you notice wrist pain, reduced grip strength, or forearm bowing. Ask your doctor to formally record this diagnosis. Any biological children carry a 50% chance of inheriting the deletion and would benefit from early growth assessment.

SHOX

Establish a Cognitive Baseline Now, in Your 30s

Your ABCA7 variant is linked at the population level to roughly double the lifetime risk of late-onset Alzheimer's disease (meta-analyses of over 149,000 people). A preliminary ITIH2 signal adds modest weight. See a neurologist for a formal baseline now. Keep blood pressure, cholesterol, and blood sugar well controlled, as vascular health directly interacts with the ABCA7 pathway. Report new memory difficulties, word-finding problems, or planning changes to your doctor promptly.

ABCA7 ITIH2

Partner Carrier Testing Is Essential Before Starting a Family

You carry single altered copies of CPT2 (metabolic muscle disease), NEB (nemaline myopathy), DUOXA2 (congenital hypothyroidism), TRIM32 (limb-girdle muscular dystrophy), and FLG2 (peeling skin syndrome). None affect your health today, but each creates a one-in-four chance of an affected child if your partner also carries a matching variant. A genetic counsellor can arrange a targeted panel and walk you through all options including preimplantation genetic testing.

CPT2 NEB DUOXA2 TRIM32 FLG2

Support Immune Balance With an Anti-Inflammatory Lifestyle

TLR10 normally brakes inflammatory signalling, and your altered copy reduces that slightly. MST1 supports immune balance in the gut lining. GSTA4 clears toxic byproducts from fat metabolism. Together, these make an anti-inflammatory diet genuinely relevant: vegetables, oily fish, whole grains, and olive oil, with less ultra-processed food. Healthy weight and regular activity support the same pathways. No urgent clinical action is needed, but these habits compound over decades.

TLR10 MST1 GSTA4

Use Gas Detectors at Home, Not Your Nose Alone

Your OR2T11 deletion removes one copy of a receptor that detects the warning odorant added to natural gas. Your remaining copy is intact, but you may need a higher concentration to notice a leak reliably. Install carbon monoxide and gas detectors on every floor, especially near appliances. Test them monthly. If you ever suspect a leak, leave the building and call your provider from outside.

OR2T11

Newborn Thyroid Screening Matters If You Have Children

Your DUOXA2 variant does not affect your own thyroid. But if your partner also carries a DUOXA2 variant, your children have a one-in-four chance of congenital hypothyroidism. This is very treatable when caught on a newborn screen but can cause permanent developmental harm if missed. Mention your carrier status to your obstetrician or midwife in advance, and make sure any newborn heel-prick result is formally reviewed.

DUOXA2

Disease-Associated Variants

We have detected disease-associated variants in **4 genes**. These variants are linked to known genetic conditions.

SHOX

DISEASE-ASSOCIATED

CONDITION	STATUS	VARIANT	PROTEIN	GENOTYPE	CLINVAR
Leri-Weill Dyschondrosteosis	LIKELY AFFECTED	X-647522-648178-G-<DEL>-DEL	NP_000442.1:5/5	N/<DEL>	Pathogenic

SHOX sits in a special stretch of your sex chromosomes called the pseudoautosomal region, shared between the X and Y. Unlike most X-chromosome genes, SHOX stays active on both sex chromosomes, so both copies normally drive bone growth. You have a deletion removing one of those copies, classified as pathogenic for Leri-Weill Dyschondrosteosis. This condition affects how the long bones in your arms and legs develop, potentially causing disproportionate limb shortening and, in some people, a wrist deformity called Madelung deformity.

WHAT THIS MEANS FOR YOU

You carry a deletion that removes one working copy of SHOX, the gene that directs bone growth, especially in the arms and legs. This causes Leri-Weill Dyschondrosteosis. At 37, your height and limb proportions are set. What stays relevant now is your wrist and forearm health: Madelung deformity, a subtle bowing or angling of the wrist, along with stiffness or aching, can still develop or worsen in adulthood. Males with the same exon 5 deletion have been documented with these features. This deletion does not affect your heart, brain, or lifespan. The most actionable point is family planning: each child you have has a 50% chance of inheriting this deletion, and early diagnosis opens the door to effective growth hormone therapy during childhood.

ASSOCIATED CONDITIONS

Leri-Weill Dyschondrosteosis

Leri-Weill Dyschondrosteosis is a skeletal dysplasia that causes disproportionate shortening of the middle segments of the limbs, primarily the forearms and lower legs, together with a characteristic wrist and forearm bone deformity called Madelung deformity. Overall height is also reduced. It is one of the most common single-gene causes of short stature and results from insufficient SHOX protein during bone development.

You have a pathogenic deletion removing one functional copy of SHOX, which is sufficient to cause Leri-Weill Dyschondrosteosis. This is a high-penetrance autosomal dominant condition, meaning one altered copy produces clinically recognisable effects. Standard-of-care guidelines for LWD apply to you, which means orthopaedic monitoring of your wrists and forearms, and referral to a clinical geneticist if you have not already been seen by one. Because you are male, your clinical expression is typically present but milder than in females. Oestrogen accelerates skeletal features such as Madelung deformity, which explains why females are more severely affected. A large review of 207 publications found that heterozygous SHOX mutations cause a mean adult height of roughly 2.2 standard deviations below average and are present in 50 to 90 percent of LWD cases (PMID: 21325865). A case report confirmed that males with exon 5 SHOX deletions do have short stature and Madelung deformity (PMID: 17028440), and a study of LWD families noted that muscular hypertrophy is a frequent finding specifically in males (PMID: 10713888). At 37, your skeletal growth is complete, so height and limb proportions will not change further. Wrist and forearm symptoms can still develop or worsen over time, however, and are worth monitoring.

SHOX-related short stature

SHOX-related short stature refers to the milder end of the SHOX haploinsufficiency spectrum, where reduced height is the primary feature without the full constellation of Madelung deformity and mesomelic limb shortening seen in Leri-Weill Dyschondrosteosis. It is a recognised diagnostic category and an FDA-approved indication for growth hormone therapy in children.

Your deletion affects SHOX in the same way as milder presentations of SHOX-related short stature. The spectrum from isolated short stature to full LWD is continuous, and clinical expression is highly variable even within the same family. One study found that affected parents in the same families had final heights ranging from 1.9 to 1.2 standard deviations below average, showing genuinely variable outcomes (PMID: 29330548). The most important practical implication now is for any children you may have. Each child faces a 50 percent chance of inheriting this deletion, and early diagnosis in childhood opens the door to growth hormone therapy, which is approved specifically for SHOX haploinsufficiency and has demonstrated effectiveness (PMID: 21325865, PMID: 35985710).

Langer Mesomelic Dysplasia

Langer Mesomelic Dysplasia is a more severe skeletal dysplasia affecting the same bones as Leri-Weill Dyschondrosteosis but causing markedly greater shortening of the forearms and lower legs. It results from having no working copies of SHOX at all, rather than just one non-working copy.

You have one working copy of SHOX, not zero, so Langer Mesomelic Dysplasia does not apply to you personally. It is relevant to family planning: if a future partner also carried a SHOX deletion, which occurs in approximately 1 in 1,000 people, there would be a 25 percent chance that a child could inherit two non-working copies and be affected by this more severe condition (PMID: 19724992). A genetics counsellor can discuss partner testing options with you.

THE BONE GROWTH INSTRUCTION PATHWAY

Why this matters: SHOX acts as a master switch inside growth-plate cells. Understanding this pathway explains why losing one copy of SHOX produces shorter, sometimes bowed limb bones, particularly in the forearms and lower legs, rather than a whole-body problem.

Think of your long bones as having a construction zone near each end called the growth plate. Special cartilage cells in this zone receive instructions telling them when to multiply, when to mature, and when to step aside so new bone can form. SHOX is one of the key instruction writers. When SHOX output is reduced, the timing and volume of these instructions goes off, and the middle segments of the limbs end up shorter and sometimes bent.

Bone growth plate
Cartilage cells in the growth plate multiply and line up, acting as a scaffold for new bone

Ends Of Long Bones In Arms And Legs

›

⚠ SHOX ACTS HERE

SHOX protein
Enters the nucleus of growth-plate cartilage cells and switches on genes that control how cells mature and when they stop dividing

Nucleus Of Hypertrophic Chondrocytes

›

NPPB signal
SHOX activates NPPB, a signalling molecule that tells cartilage cells to mature in an orderly, timed way

Bone-Forming Cells

›

Cartilage cell maturation
Mature cartilage cells signal for calcium deposits, converting the cartilage scaffold into solid bone

Growth Plate

⌄

New bone
Solid bone replaces cartilage, lengthening the limb segment

Shaft Of Long Bones

When this pathway is impaired:

With reduced SHOX, the instruction signal in step 2 is weaker than normal, disrupting orderly cartilage cell maturation, primarily in the forearm and lower-leg bones, resulting in shorter and sometimes bowed bones and wrist deformity.

SYMPTOMS TO WATCH

- **Wrist pain, stiffness, or reduced range of motion**

  Madelung deformity causes abnormal geometry of the radius and ulna at the wrist. In adults this can become progressively symptomatic, causing pain, reduced grip strength, or difficulty rotating the forearm. This is the most directly actionable musculoskeletal symptom in an adult male with LWD.

  ☑ **Action:** *See your GP or a hand and wrist orthopaedic surgeon for assessment. X-rays of the wrist can confirm the presence and degree of Madelung deformity. Non-surgical options include physiotherapy and splinting; surgical correction is available for severe cases.*

- **Forearm bowing or visible asymmetry in limb contour**

  Progressive bowing of the radius can become more apparent in adulthood and may contribute to functional limitations. In a multicentric study of 144 children with SHOX haploinsufficiency, Madelung deformity was present in 36 percent of SHOX-positive patients compared with 10 percent of those without the variant.

  ☑ **Action:** *Point this out to your doctor at your next routine appointment. A baseline wrist and forearm X-ray provides a useful reference point for monitoring over time.*

- **Elbow pain or reduced elbow extension**

  Altered elbow angle, known as cubitus valgus, is a recognised skeletal feature of LWD resulting from mesomelic bone changes. While less common than wrist features in males, it has been documented as part of the LWD phenotype.

  ☑ **Action:** *Mention to your doctor if you notice asymmetry, pain, or restricted movement at the elbow. Orthopaedic review is appropriate if it becomes functionally limiting.*

- **Unexplained breathlessness or fatigue on exertion**

  Emerging zebrafish research suggests that SHOX deficiency may increase cardiac stress markers, specifically elevated NPPB in heart tissue. The study authors recommend that people with SHOX deficiency be monitored for cardiac disease in later life. This is preclinical evidence, not yet confirmed in large human studies, but worth keeping on your radar.

  ☑ **Action:** *Report any new or worsening breathlessness, chest discomfort, or unexplained fatigue to your doctor promptly. Routine cardiovascular health checks including blood pressure and cholesterol are good practice regardless.*

KEY ACTIONS

See a clinical genetics team so you and any future children can be properly assessed. Any child found to carry this deletion should see a pediatric endocrinologist early, since growth hormone therapy works best when started during the growth years. For your own health, see an orthopedic or sports medicine physician if you notice wrist pain, forearm stiffness, or reduced grip strength. Targeted wrist mobility and strengthening exercises help maintain function, and a physiotherapist can tailor a plan to your anatomy. Avoid heavy repetitive wrist loading if it causes discomfort. Let close relatives know a genetic test is available, as siblings or parents may be undiagnosed.

CPT2

DISEASE-ASSOCIATED

CONDITION	STATUS	VARIANT	PROTEIN	GENOTYPE	CLINVAR
Carnitine Palmitoyltransferase Deficiency	LIKELY CARRIER	rs74315294	NP_000089.1:p.Ser113Leu	C/T	Pathogenic

VARIANT POPULATION FREQUENCY: 2/1,000

Your CPT2 gene makes an enzyme on the inner mitochondrial membrane that performs the final step of the carnitine shuttle, converting fat parcels into a form the cell can burn for energy. Without this step, fat accumulates unused and muscle, heart, and liver run short of fuel under stress. CPT2 deficiency is autosomal recessive (ClinGen Definitive), so two disrupted copies are typically needed for the full disorder. You carry one altered copy and one working copy, which is why this result is described as a likely carrier.

WHAT THIS MEANS FOR YOU

You carry one copy of the S113L variant in CPT2, an enzyme that helps burn long-chain fats for energy in muscle cells. Because this is a recessive condition, your one working copy is generally protective and most single-copy carriers feel well day-to-day. Even so, published studies document a minority who experienced muscle pain or weakness during intense exercise, fasting, or fever, partly because the S113L enzyme loses activity more readily when body temperature rises. The most important practical step is family planning: if your partner carries a CPT2 variant, each pregnancy has a one-in-four chance of two disrupted copies. Your Ashkenazi Jewish ancestry makes partner testing especially worthwhile, as a second founder CPT2 variant is more common in this population.

ASSOCIATED CONDITIONS

Carnitine Palmitoyltransferase II Deficiency, Myopathic Form

Carnitine Palmitoyltransferase II (CPT2) deficiency in its adult myopathic form is a disorder of long-chain fatty acid metabolism. The body cannot efficiently use fat as a fuel source during high-demand situations, leading to recurrent episodes of muscle breakdown (rhabdomyolysis), muscle pain, stiffness, and dark urine, typically triggered by prolonged exercise, fasting, fever, or other metabolic stress.

You carry one copy of the S113L variant, the single most common pathogenic CPT2 change, found on roughly half of all disease-causing CPT2 alleles (PMID: 15363638). Because CPT2 deficiency follows an autosomal recessive pattern, you are a heterozygous carrier. One working copy is generally protective, and most people in your situation remain completely asymptomatic day-to-day. That said, published case series specifically documenting S113L have reported a minority of heterozygotes who developed symptoms such as muscle pain or exercise-related episodes under metabolic stress, including prolonged exercise, fasting, or fever (PMID: 10090476, PMID: 20810031). This happens partly because the S113L enzyme is thermolabile: it loses activity more readily when your body temperature rises. So while full CPT2 deficiency is very unlikely for you, it is worth knowing your triggers and alerting your doctors. The most important practical implication right now is family planning: if your partner also carries a CPT2 variant, each pregnancy would have a one-in-four chance of inheriting two disrupted copies. Given your Ashkenazi Jewish ancestry, a second founder variant called 413delAG is found at higher frequency in this population (PMID: 10090476), making it especially worthwhile to discuss partner testing with your genetic counsellor.

Carnitine Palmitoyltransferase II Deficiency

CPT2 deficiency is a spectrum disorder of mitochondrial fatty acid oxidation caused by reduced or absent activity of the CPT2 enzyme. Depending on the severity of the enzyme disruption, it can range from the adult-onset muscular form through to severe infantile and lethal neonatal forms characterised by low blood sugar, cardiac involvement, and multi-organ disease.

Your variant is classified as Pathogenic in ClinVar for this broader disease spectrum. As a heterozygous carrier for an autosomal recessive condition, you are not expected to develop the severe infantile or neonatal forms, which require both copies of the gene to be disrupted. Your relevance to this broader label is primarily as a carrier for family planning purposes, and as someone who should stay aware of the adult stress-related phenotype described above.

THE CARNITINE SHUTTLE

Why this matters: CPT2 performs the final, essential step of the carnitine shuttle, the only route by which long-chain fats can cross into the mitochondrial fat-burning engine. Without this step, fat cannot become fuel in the body's most energy-hungry tissues.

Think of your mitochondria as a furnace that burns fat for fuel. Long-chain fat molecules are too big to enter the furnace door on their own, so they get wrapped in a carrier molecule called carnitine to get through. CPT2 is the worker just inside the door whose job is to unwrap the fat so it can actually be burned. If CPT2 is not working well, wrapped parcels pile up and the furnace runs short of fuel.

Long-chain fatty acid
A long-chain fat molecule arrives in the cell from the bloodstream and is activated into a form ready for processing

Cell Cytoplasm

›

CPT1 (outer gate enzyme)
Attaches a carnitine molecule to the activated fat, creating an acylcarnitine parcel that can cross the mitochondrial outer membrane

Outer Mitochondrial Membrane

›

Carnitine translocase
Shuttles the acylcarnitine parcel across the inner mitochondrial membrane into the matrix

Inner Mitochondrial Membrane

›

⚠ CPT2 ACTS HERE

CPT2 (inner gate enzyme)
Removes the carnitine wrapper, releasing the fat as acyl-CoA so it can be burned. This is the step affected by your variant.

Inner Mitochondrial Membrane, Matrix Side

⌄

Beta-oxidation machinery
Breaks down the unwrapped fat step by step to generate energy (ATP) for the cell

Mitochondrial Matrix

When this pathway is impaired:

When CPT2 activity is reduced, acylcarnitine parcels accumulate unprocessed, fat cannot be burned efficiently, and energy-hungry tissues like muscle run low on fuel during exercise, fasting, or illness.

DOCUMENTED TRIGGERS

- **Prolonged or intense exercise**

  The adult myopathic form of CPT2 deficiency is classically triggered by prolonged exercise, which forces the body to rely heavily on fat burning once glycogen stores are exhausted. Published cohorts of over 200 affected families identify exercise as the primary trigger for rhabdomyolysis episodes (PMID: 15363638, PMID: 10607472). A case series of 59 individuals, including heterozygotes for S113L, also documented exercise as a precipitant (PMID: 10090476).

- **Fasting or prolonged caloric restriction**

  Fasting depletes glucose reserves and forces the body to switch almost entirely to fat as its primary fuel, placing maximum demand on the CPT2 enzyme. Fasting is documented as a trigger across multiple cohort studies and reviews (PMID: 15363638, PMID: 10607472, PMID: 30401918). A heterozygous sister carrying S113L alone experienced fasting-induced hypoglycaemia (PMID: 12362414).

- **Fever or elevated body temperature**

  The S113L enzyme is thermolabile, meaning it loses function more readily at elevated temperatures than the normal enzyme. Fever is documented as a specific trigger for CPT2-related episodes and is mechanistically tied to this thermolability (PMID: 32129275, PMID: 15363638).

- **Intercurrent illness or infection**

  Illness combines multiple stressors: fever, reduced food intake, and increased metabolic demand. Metabolic myopathy cohort data confirm illness as a documented precipitant for rhabdomyolysis in CPT2-related conditions (PMID: 37859320, PMID: 30401918).

- **Environmental temperature extremes (cold or intense heat)**

  Environmental temperature stress is listed among documented triggers for CPT2 deficiency episodes, consistent with the enzyme's thermolability. Both cold exposure and extreme heat have been noted in clinical descriptions of trigger patterns (PMID: 32129275).

- **Anesthesia and surgical stress**

  Anesthesia and perioperative metabolic stress are recognised triggers in fatty acid oxidation disorders including CPT2 deficiency, given the combination of prolonged pre-operative fasting and the physiological stress response. This is documented in clinical guidance for managing CPT2 and related fatty acid oxidation disorders (PMID: 15363638, PMID: 30401918).

SYMPTOMS TO WATCH

- **Muscle pain, stiffness, or cramping during or after exercise**

  Reduced CPT2 enzyme activity means muscles cannot efficiently access fat for fuel during sustained effort. When glycogen runs low, muscle cells may be starved of energy, leading to pain and damage. Even in single-copy heterozygotes for S113L, this has been reported under metabolic stress (PMID: 10090476).

  ☑ **Action:** *Rest immediately and hydrate well. If pain is severe, spreads to large muscle groups, or is accompanied by dark urine, seek medical attention the same day and mention your CPT2 variant.*

- **Dark, brown, or cola-coloured urine after exercise or illness**

  Dark urine during or after exertion is the hallmark warning sign of myoglobinuria, muscle protein leaking into the bloodstream and filtering through the kidneys. This indicates significant muscle breakdown (rhabdomyolysis) and can cause acute kidney injury if not treated promptly. This is the most serious acute complication documented in CPT2 deficiency (PMID: 15363638).

  ☑ **Action:** *Go to an emergency department immediately. Tell the team about your CPT2 variant and ask them to check creatine kinase (CK), kidney function, and urine myoglobin. Intravenous fluids are often needed to protect the kidneys.*

- **Generalised muscle weakness during or after fever or illness**

  Because the S113L enzyme is thermolabile, a fever can reduce your already partial CPT2 activity further, impairing fat metabolism in muscle precisely when the body needs it most (PMID: 32129275).

  ☑ **Action:** *Rest, stay well hydrated, and make sure you are taking in carbohydrate-containing foods or fluids to spare fat metabolism. If weakness is severe or accompanied by dark urine, seek emergency care.*

- **Unusual exercise intolerance — tiring much faster than expected**

  Exercise intolerance is documented in CPT2 deficiency cohorts (reported in over half of affected patients), and has also been noted in a subset of heterozygotes under metabolic stress (PMID: 37859320, PMID: 10090476).

  ☑ **Action:** *Note when this occurs (duration of exercise, recent eating, temperature, illness) and discuss with your doctor. A supervised incremental exercise test and CK measurement can help determine whether your CPT2 variant is contributing.*

KEY ACTIONS

See a genetics or metabolic specialist, especially before planning a family, so your partner can be offered CPT2 carrier testing. Avoid prolonged fasting and eat carbohydrate-rich meals before and during sustained exercise, since carbs reduce reliance on fat burning. During fever or illness, stay well-fed and hydrated. Before any surgery, tell your anaesthetist about this variant. If you notice muscle pain, weakness, or dark urine during or after exercise or illness, seek prompt medical care as these may signal rhabdomyolysis.

DUOXA2

DISEASE-ASSOCIATED

CONDITION	STATUS	VARIANT	PROTEIN	GENOTYPE	CLINVAR
Thyroid Dyshormonogenesis	LIKELY CARRIER	rs201506037	Altered protein assembly	T/C	Pathogenic

VARIANT POPULATION FREQUENCY: 3/10,000

DUOXA2 is your thyroid gland's logistics coordinator. Its protein escorts DUOX2 to the cell surface where it generates hydrogen peroxide, the chemical spark needed to attach iodine to thyroglobulin and build thyroid hormones. You have one altered and one working copy, making you a heterozygous carrier of this autosomal recessive condition. Pedigree studies consistently show that one working copy maintains normal thyroid function. This variant is most relevant for family planning.

WHAT THIS MEANS FOR YOU

You carry one altered copy of DUOXA2, the gene that escorts a key enzyme to the right spot in your thyroid cells so they can produce hydrogen peroxide and, in turn, thyroid hormones. Because this follows an autosomal recessive pattern, your one working copy is enough to keep your thyroid running normally. Studies consistently show that people with one DUOXA2 variant have normal thyroid hormone levels. Your personal risk from this variant alone is low. Where it matters most is family planning: if a future co-parent also carries a DUOXA2 variant, a child could inherit two non-working copies and be at risk for congenital hypothyroidism, which is caught by newborn screening and manageable with daily thyroid hormone tablets.

ASSOCIATED CONDITIONS

Thyroid Dyshormonogenesis

Thyroid dyshormonogenesis is a group of inherited conditions in which the thyroid gland is structurally present but cannot manufacture thyroid hormones efficiently, usually because one of the enzymes or transport proteins in the hormone-production chain is faulty. It is a leading cause of congenital hypothyroidism, presenting at or shortly after birth with elevated TSH on newborn screening, and in some cases with an enlarged thyroid gland (goiter).

You have one working copy and one altered copy of DUOXA2. Multiple human pedigree and cohort studies consistently show that people in this situation have completely normal thyroid function and pass standard newborn TSH screening without issue, because the single working copy is enough to keep the DUOX2 pathway running (PMID: 18042646, PMID: 31172499). As a heterozygous carrier of an autosomal recessive condition, your personal risk of developing thyroid dyshormonogenesis is considered low. Where this variant matters most is family planning: if a future co-parent also carries a DUOXA2 variant, each pregnancy would carry a 25% chance of inheriting two non-working copies, which can cause congenital hypothyroidism. That condition is caught by routine newborn screening and is very treatable with daily thyroid hormone replacement. One 2025 study also identified rare cases where a single DUOXA2 variant combined with a variant in a second thyroid gene contributed to congenital hypothyroidism through a digenic mechanism (PMID: 39787321). This is not yet established as a common pathway, but it is worth raising with your doctor if you have any personal or family history of thyroid disease.

Congenital Hypothyroidism

Congenital hypothyroidism is the most common neonatal endocrine disorder, caused by insufficient thyroid hormone production from birth. Without early treatment it can impair brain development and growth, but when identified through newborn screening and treated promptly with levothyroxine, outcomes are typically excellent.

Congenital hypothyroidism caused by biallelic DUOXA2 loss-of-function is the same condition described above under thyroid dyshormonogenesis. The same reasoning applies to you: as someone carrying one altered copy, you are not expected to develop congenital hypothyroidism yourself (PMID: 18042646, PMID: 31172499). The relevance is to any children you may have in the future. If your co-parent is found to carry a DUOXA2 variant, pre-conception or prenatal genetic counselling would be valuable so that newborn screening and early treatment can be planned in advance.

Transient Congenital Hypothyroidism

Transient congenital hypothyroidism is a temporary form of low thyroid function present at birth that resolves on its own, sometimes within weeks to years. It can still require short-term treatment with levothyroxine in early infancy to protect brain development during the window when the thyroid is not yet producing enough hormone.

The clinical spectrum of congenital hypothyroidism linked to biallelic DUOXA2 mutations ranges from permanent to transient forms, and some children with two non-working copies recover normal thyroid function by early childhood (PMID: 30599477, PMID: 32252219). This range is relevant to genetic counselling for offspring rather than to your own health. As someone with one working copy, you are not at risk of transient congenital hypothyroidism yourself based on current evidence.

THYROID HORMONE SYNTHESIS

Why this matters: This is the core pathway through which your thyroid gland assembles its hormones. DUOXA2 sits at one of the most essential steps: delivering the chemical spark-maker to its workstation so that iodine can be built into thyroid hormones.

Think of your thyroid follicle cells as a small factory. They pull iodine from the blood and need a chemical spark to attach that iodine to a protein scaffold called thyroglobulin. DUOXA2 is the delivery worker who carries the spark-maker (DUOX2) to the right workbench. Without the delivery, the spark-maker sits idle inside the cell, the iodine goes unattached, and no hormone gets made.

Iodine transporter
Iodine from food is pulled from the blood into thyroid follicle cells through a dedicated pump on the cell's base

Basolateral Cell Membrane

DUOX2 protein
DUOX2 is built inside the cell in a compartment called the endoplasmic reticulum, where it must be properly folded before it can be used

Endoplasmic Reticulum

⚠ DUOXA2 ACTS HERE

DUOXA2 chaperone
DUOXA2 binds to DUOX2, stabilises it, and escorts it from inside the cell to the surface of the thyroid cell that faces the follicle lumen

Endoplasmic Reticulum To Apical Membrane

DUOX2 at cell surface
Once at the surface, DUOX2 generates a controlled burst of hydrogen peroxide and releases it into the follicle lumen

Apical Cell Membrane

Thyroid peroxidase
Using the hydrogen peroxide as its fuel, this enzyme attaches iodine atoms onto the protein scaffold thyroglobulin

Follicle Lumen

Thyroid hormones T3 and T4
The iodinated thyroglobulin is processed and finished thyroid hormones are released into the bloodstream to regulate energy, growth, and metabolism

Bloodstream

When this pathway is impaired:

When DUOXA2 cannot escort DUOX2, the spark-maker stays trapped inside the cell, hydrogen peroxide is not made at the right place, and iodine cannot be attached to thyroglobulin, so thyroid hormone production stalls.

KEY ACTIONS

Let your doctor know about this variant, especially if you are planning children. Genetic counselling is recommended so a counsellor can arrange partner testing and explain what combined results would mean for your children. If you have children, ensure their newborn thyroid screening result is followed up. If you ever notice unexplained fatigue, weight changes, or cold intolerance, ask your doctor to check thyroid function and mention this variant. An emerging finding suggests one DUOXA2 variant combined with a second thyroid-gene variant may rarely contribute to mild hypothyroidism, so share your full genetic picture with any thyroid specialist.

NEB

DISEASE-ASSOCIATED

CONDITION	STATUS	VARIANT	PROTEIN	GENOTYPE	CLINVAR
Nemaline Myopathy	LIKELY CARRIER	2-151598566-151609129-T-<DEL>-DEL	NP_001157980.2:82-89/182	N/<DEL>	Pathogenic

NEB produces nebulin, a giant protein inside your muscle sarcomeres that acts as a molecular ruler, controlling the precise length of the thin filaments muscles need to generate force. Without enough working nebulin (in people with two altered copies), muscles cannot contract properly, causing nemaline myopathy. You carry one pathogenic deletion in NEB. Because this condition is autosomal recessive, your intact second copy compensates fully, and the literature does not document muscle symptoms in people carrying a single small NEB deletion like yours.

WHAT THIS MEANS FOR YOU

You carry one altered copy of NEB, the gene that makes nebulin, a structural protein that keeps your muscle fibres working precisely. Because nemaline myopathy is recessive, two non-working copies are needed for the condition to develop. With one intact copy still producing nebulin, your muscles are expected to work normally. This variant matters most for family planning: if a future partner also carries a pathogenic NEB variant, each pregnancy has a one-in-four chance of developing nemaline myopathy. Your 8-exon deletion is well below the 52-to-97-exon range tied to a rarer dominant form of myopathy, so that concern does not apply here. If you ever notice unexplained weakness in your hands, feet, or lower legs, mention this variant to your doctor.

ASSOCIATED CONDITIONS

Nemaline Myopathy

Nemaline myopathy is a rare inherited muscle disorder present from birth or early childhood. It is characterised by muscle weakness and low muscle tone (hypotonia), with tiny rod-shaped protein clumps called nemaline bodies visible in muscle tissue under a microscope. Severity ranges from very mild, where independent walking is achieved, to severe forms involving profound weakness, breathing difficulties, and swallowing problems (PMID: 31228046).

You carry one pathogenic deletion spanning exons 82 to 89 of your NEB gene. Because nemaline myopathy caused by NEB variants follows an autosomal recessive pattern, two non-working copies are required to develop the disease. Your second NEB copy is intact and producing nebulin normally. In a study covering 159 families with pathogenic NEB variants, people who carried a single variant like yours were unaffected (PMID: 25205138). A 2025 study found that very large NEB deletions spanning 52 to 97 exons on just one copy were linked to a milder, dominantly inherited distal myopathy in some families (PMID: 40517164). Your deletion spans 8 exons, considerably smaller than that range, and current evidence does not place your variant in that dominant-risk category. The most clinically important implication for you right now is family planning: if your partner also carries a pathogenic NEB variant, each pregnancy would have a 1-in-4 chance of inheriting two non-working copies and developing nemaline myopathy. Partner testing and genetic counselling before conception are strongly recommended.

Arthrogryposis Multiplex Congenita

Arthrogryposis multiplex congenita is a condition present at birth in which multiple joints are fixed in bent or stiffened positions, limiting movement. It arises when reduced or absent fetal movement during pregnancy causes joints to stiffen, and it is associated with several genetic causes including severe forms of NEB-related muscle disease where the fetus cannot move normally in the womb (PMID: 29274205).

Arthrogryposis in the context of NEB occurs only in severe biallelic disease, where muscle function is so impaired that a fetus cannot move normally in the womb. Because you carry only one pathogenic NEB variant, this condition is not a personal health risk for you. It becomes relevant in the family planning context: if a future pregnancy were to inherit two non-working NEB copies, severe forms of NEB-related disease including arthrogryposis are among the possible outcomes. Discussing this with a genetic counsellor before you try to conceive is the right next step.

THE SARCOMERE CONTRACTION PATHWAY

Why this matters: Nebulin sits at the heart of sarcomere function, physically governing the length of the actin thin filaments that muscle fibres use to generate pulling force. When both gene copies are lost, this molecular ruler disappears and the filaments become too short and disorganised to produce meaningful contraction.

Think of a muscle fibre as a tiny rowing team. The actin filaments are the oars, and the myosin filaments are the rowers pulling them. Nebulin is the bracket keeping every oar exactly the right length so each rower gets a firm grip. When both copies of nebulin are missing, the oars are too short and uneven, so the rowers can barely pull, producing profound muscle weakness.

⚠ NEB ACTS HERE

Nebulin protein

Anchors to the Z-disk end wall of each sarcomere and extends alongside the actin thin filament like a measuring tape, setting its correct length

Sarcomere Z-Disk, Skeletal Muscle Fibre

›

Actin thin filament

Grows to the precise length that nebulin sets; nebulin binds and stabilises it along its full length

Sarcomere, Skeletal Muscle Fibre

›

Myosin thick filament

Reaches out and grabs the actin filament; the overlap between the two determines how much force can be produced

Sarcomere Centre, Skeletal Muscle Fibre

›

Cross-bridge cycling

Myosin pulls actin inward in repeated power strokes, shortening the sarcomere and producing contraction

Sarcomere, Skeletal Muscle Fibre

⌄

Muscle force output

Thousands of sarcomeres working together in series and parallel produce coordinated movement and breathing

Whole Muscle

When this pathway is impaired:

Without nebulin acting as a ruler (in biallelic disease), actin filaments grow too short and unevenly, reducing the myosin-actin overlap needed for force generation and causing profound muscle weakness.

SYMPTOMS TO WATCH

- **Unexplained weakness in the hands, lower legs, or feet**

  While not documented for small heterozygous NEB deletions, a 2025 study linked very large single-copy NEB deletions spanning 52 to 97 exons to a milder dominantly inherited distal myopathy. Your 8-exon deletion is well below that size range, but this is an emerging area of research. Reporting any unexplained distal weakness allows your doctor to assess whether your NEB variant could be contributing.

  ☑ **Action:** *Mention your NEB variant to your doctor and ask for a neuromuscular review. No emergency action is needed.*

KEY ACTIONS

The most important step is partner carrier testing for NEB variants before or during family planning. If your partner also carries a pathogenic NEB variant, each pregnancy would have a one-in-four chance of inheriting two non-working copies and developing nemaline myopathy. A genetic counsellor can walk you through options including preimplantation genetic testing. Informing your biological siblings and parents is also worthwhile, as they may carry the same deletion. If you ever notice unexplained distal muscle weakness, mention this variant to your doctor.

Loss-of-Function Variants

We have detected loss-of-function variants in **31 genes**. These variants reduce or eliminate the function of a gene.

ABCA7

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Brain amyloid clearance	IMPACTFUL	rs201060968	NP_061985.2:p.Trp1214Ter	G/A	High Impact

VARIANT POPULATION FREQUENCY: 2/1,000

ABCA7 is a membrane transporter that flips specific fats across cell membranes and helps brain immune cells (microglia) clear amyloid-beta, the protein that accumulates in Alzheimer's disease. You have one copy of a variant that introduces a premature stop signal, so that copy likely produces no working protein. Your other copy still functions, leaving activity reduced but not absent. Across studies of over 100,000 people, this class of ABCA7 variant consistently raises late-onset Alzheimer's risk roughly 2-fold. That is a meaningful signal, not a certainty.

GENE EXPRESSION

Most active in: Spleen, Lung, Pancreas, Kidney, Colon

WHAT THIS MEANS FOR YOU

You carry one copy of a premature stop variant in ABCA7, a gene that keeps neuronal membranes stocked with fats and helps the brain's clean-up cells remove amyloid waste. This is not a benign finding. Large studies consistently link heterozygous loss-of-function variants in this gene to roughly a 2-fold higher lifetime risk of late-onset Alzheimer's disease at the population level. That said, this is a risk modifier, not a certainty. The Mayo Clinic study that included your specific variant found cognitive onset ranging from 56 to 92 years, and many variant carriers remained cognitively healthy. Your APOE genotype and lifestyle factors, especially cardiovascular health and sleep, will also shape your trajectory. Knowing this at 37 gives you real lead time to act.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Alzheimer disease

Alzheimer's disease is the most common cause of dementia, a progressive brain condition that gradually impairs memory, thinking, language, and the ability to carry out everyday tasks. It is caused by the slow build-up of amyloid plaques and tau tangles in the brain, damaging nerve cells over time. It typically begins in later life, most often after age 60, and advances over years to decades.

- **You have a heterozygous premature stop variant in ABCA7, meaning one of your two copies of this gene produces a non-functional protein. This is not a benign situation. ABCA7 helps brain cells clear amyloid waste and maintain healthy membrane fats. When one copy is silenced, amyloid builds up faster and neuronal energy suffers. Large studies across Icelandic, European, and US cohorts consistently find that having an ABCA7 loss-of-function variant is associated with roughly a 2-fold higher risk of late-onset Alzheimer's disease compared to the general population (PMID: 25807283; PMID: 29782324). A meta-analysis of 149,580 people put the odds ratio at approximately 1.78 (PMID: 29782324). Your specific variant, p.Trp1214Ter, was directly included in Mayo Clinic deep-phenotyping of 5,353 individuals; among those who developed symptoms, onset ranged from 56 to 92 years, with a mean of 75.6 years (PMID: 35047668). Importantly, many people with this variant in control cohorts remained cognitively healthy, confirming that this is a risk modifier with incomplete penetrance, not a certainty. Your APOE genotype, cardiovascular health, sleep quality, and physical activity all interact significantly with this risk. Having one copy of this variant meaningfully increases your lifetime risk of Alzheimer's disease, though most people with this variant do not develop the disease. Family history strongly modifies this risk, and enhanced monitoring is typically recommended. Starting that process now, at 37, gives you the longest possible window to act.**

Dementia

Dementia is a broad syndrome affecting memory, thinking, and social abilities severely enough to interfere with daily life. It is not a single disease but a collection of symptoms caused by various brain conditions, with Alzheimer's disease being the most common underlying cause. Other forms include vascular dementia, which involves reduced blood flow to the brain, and frontotemporal dementia, which primarily affects behaviour and language.

ABCA7 loss-of-function variants are enriched in both late-onset and early-onset dementia cohorts beyond Alzheimer's disease alone (PMID: 34090711). Belgian neuropathology data on premature termination codon variants specifically, like yours, found that a minority of affected individuals developed vascular dementia or cerebral amyloid angiopathy alongside or instead of classic Alzheimer's pathology, and non-amnestic features such as language difficulties, executive dysfunction, and behavioural changes were seen in 18% of those with premature stop variants (PMID: 41494406). This means the range of what you might notice, if symptoms ever develop, is broader than memory loss alone. Knowing this helps you and your doctors act quickly if something feels different, rather than dismissing an unfamiliar symptom as unrelated.

BRAIN AMYLOID CLEARANCE AND NEURONAL LIPID BALANCE PATHWAY

Why this matters: ABCA7 sits at the intersection of two processes central to Alzheimer's disease: keeping neuronal membranes and mitochondria properly fuelled with the right fats, and coordinating the brain's immune clean-up of amyloid-beta. Reduced activity from your variant affects both arms simultaneously.

Think of ABCA7 as a two-job worker stationed at cell membranes. One job is to keep the membrane's fatty layers properly stocked and supply the cell's power plants (mitochondria) with fats they need for energy. The second job is to help the brain's clean-up crew (microglia) break down amyloid waste. When this worker is less active, membranes become unstable, power plants run less efficiently, and amyloid debris accumulates over time.

Cell membrane phospholipids
Phosphatidylserine and phosphatidylcholine are made inside the cell and sit on the inner face of the membrane, waiting to be moved.

Inner Leaflet Of Cell Membrane

⚠ ABCA7 ACTS HERE

ABCA7 transporter
ABCA7 uses ATP energy to flip these fats to the outer face of the membrane and export them to lipid-carrier proteins like APOA1, keeping the membrane balanced and supplying fats to mitochondria.

Cell Membrane, Golgi, Early Endosomes

Neuronal membranes and mitochondria
With proper lipid balance, neuron membranes stay structurally sound, mitochondria generate energy efficiently, and synapses fire normally.

Neurons Throughout The Brain

Amyloid precursor protein (APP)
APP sits in the neuronal membrane. Normal ABCA7 activity slows the rate at which APP is pulled inside the cell for processing, limiting amyloid fragment output.

Neuronal Cell Membrane And Endosomes

Amyloid-beta fragments
When APP is processed inside the cell, small sticky fragments called Aβ are released. Normally only small amounts accumulate and the rest are cleared.

Brain Tissue And Synapses

Microglia (brain clean-up cells)
Microglia use ABCA7 to help recognise, engulf, and break down Aβ deposits while keeping inflammatory responses appropriately tuned.

Brain Tissue

Amyloid plaque accumulation
If Aβ production is elevated and clearance is reduced together, amyloid deposits build up over years to decades, a core feature of Alzheimer's pathology.

Brain Tissue

When this pathway is impaired:

Reduced ABCA7 activity raises Aβ production, weakens microglial clearance, depletes neuronal membrane fats, and impairs mitochondrial energy, a slow-building combination that elevates late-onset Alzheimer's risk.

SYMPTOMS TO WATCH

- **Progressive memory difficulties, particularly trouble recalling recent events, conversations, or appointments**

  Memory impairment was the most common initial symptom reported in the Mayo Clinic deep-phenotyping study of ABCA7 loss-of-function variant carriers, including p.Trp1214Ter specifically. Catching this early maximises the window for intervention.

  Action: *Report any noticeable, persistent decline in memory to your doctor. Request a formal cognitive assessment, and ask about early referral to a neurologist or memory clinic.*

- **Language difficulties, word-finding problems, or trouble following conversations**

  Non-amnestic features including language dysfunction were documented in 18% of people with premature termination codon variants in ABCA7 in a Belgian cohort, making this a recognised early signal for this specific variant class.

  ☑ **Action:** *Discuss with your doctor if you notice these changes persisting over weeks. A neuropsychological assessment can distinguish normal variation from something that warrants further investigation.*

- **Executive function changes, such as difficulty planning, organising, or making decisions that feel new or worsening**

  Dysexecutive presentation was reported alongside classic amnestic features in a subset of ABCA7 premature termination codon carriers. These changes can be subtle at first and are worth tracking over time.

  ☑ **Action:** *Note any patterns that feel new and persist over weeks. Mention them at your next medical appointment, or sooner if they are affecting daily life.*

- **New or worsening depression, especially if it emerges in mid-to-later life without a clear life-event cause**

  The Mayo Clinic study found depression rates of 41.6% among ABCA7 loss-of-function variant carriers, substantially higher than the general population. Depression can be an early neuropsychiatric signal preceding cognitive decline, or an independent feature of this variant's phenotype.

  ☑ **Action:** *Do not dismiss new depression as unrelated. Mention it to your doctor and ask that your cognitive baseline be tracked. Effective treatment of depression also supports brain health.*

- **Unexplained behavioural or personality changes noticed by family or close friends**

  A small number of ABCA7 loss-of-function carriers have presented with a behavioural syndrome resembling frontotemporal dementia rather than classic Alzheimer's. Family observations are often the first clue to these early changes.

  ☑ **Action:** *Take family members' observations seriously. A neurological evaluation is warranted if these changes are persistent or escalating.*

KEY ACTIONS

Share this result with your primary care doctor and ask about a referral to a neurologist or memory specialist to establish a cognitive baseline now, in your 30s, as a reference point for the future. Report any new memory difficulties, word-finding problems, mood shifts, or trouble with planning promptly. Ask your doctor whether APOE genotyping makes sense for you, as it adds important context. Keep cardiovascular risk factors, blood pressure, cholesterol, and blood sugar well controlled, since these interact with ABCA7 biology to shape long-term brain health.

ITIH2

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Cell matrix stability	IMPACTFUL	rs151229507	Altered protein assembly	G/C	High Impact

VARIANT POPULATION FREQUENCY: 3/1,000

Your liver produces the ITIH2 protein and releases it into your bloodstream, where it travels to tissues and acts like a fastener, locking onto a gel-like substance called hyaluronan that fills the spaces between cells. This keeps tissue scaffolding stable and helps regulate inflammation. ITIH2 is frequently switched off inside established cancer cells, making it a candidate tumour-suppressor. No confirmed inherited disease has been defined for germline variants in this gene, and population genetics data suggest one altered copy is well tolerated.

GENE EXPRESSION

Most active in: Liver · Kidney · Lung · Spleen · Pancreas

WHAT THIS MEANS FOR YOU

You have one altered copy of ITIH2, a gene your liver uses to produce a protein that helps anchor the gel-like scaffold between your cells, keeping tissues organised and inflammation in check. Because the gene tolerates this kind of variation well at the population level, this does not point to a known inherited disease. Research does suggest ITIH2 may help restrain tumour spread and has preliminary links to metabolic and neurodegenerative conditions, but none of these signals have been confirmed as actionable germline risks for someone with one altered copy. Think of this as a finding worth keeping on your radar and discussing with your doctor, rather than something requiring urgent action today.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Cancer susceptibility — extracellular matrix tumour suppressor role (ITIH2-associated)

Several common solid tumours, including breast, colon, and lung cancer, frequently show loss of ITIH2 expression in tumour tissue. ITIH2 is considered a candidate tumour-suppressor gene based on its role in stabilising the extracellular matrix scaffold that normally restrains abnormal cell movement and invasion.

Your variant reduces the amount of functional ITIH2 protein you make. In the general population, ITIH2's LOEUF score of 1.16 and near-zero pLI indicate the gene tolerates one altered copy without a well-defined clinical syndrome. The tumour-suppressor evidence comes almost entirely from somatic (acquired) loss inside tumour cells, not from germline variants like yours. No study has shown that a single germline loss-of-function variant in ITIH2 meaningfully raises cancer risk on its own. This association is biologically plausible but has not been validated as an actionable germline risk factor. The most practical step is to keep up with standard cancer screening recommended for your age and sex — not because this variant demands extra surveillance, but because routine screening is valuable for everyone.

Neurodegenerative disease — Alzheimer disease preliminary association (ITIH2-associated)

Alzheimer disease is a progressive neurodegenerative condition that gradually impairs memory and cognitive function. It has complex genetic and environmental causes, and many genes contribute modestly to overall risk.

A small whole-genome sequencing study in Caribbean Hispanic families found a rare synonymous ITIH2 variant that co-segregated with Alzheimer disease status in affected families (PMID: 32637632). This is a single, preliminary, unreplicated signal. Your variant is a different type of change — a high-impact loss-of-function variant rather than a synonymous one — and no study has measured how a germline loss-of-function variant like yours affects Alzheimer risk. There is not enough evidence to say your variant meaningfully changes your personal risk of dementia. Maintaining cardiovascular health, staying mentally and physically active, and managing metabolic health remain the most evidence-backed steps anyone can take.

Type 2 diabetes mellitus — metabolic association (ITIH2-associated)

Type 2 diabetes is a chronic metabolic condition in which the body does not use insulin effectively, leading to elevated blood glucose levels over time. It is influenced by a combination of genetic predisposition and lifestyle factors.

One proteomics study found that ITIH2 protein levels in plasma extracellular vesicles were elevated in glucose-intolerant middle-aged men compared with men who had normal blood sugar (PMID: 33587339). ITIH2 is also expressed in pancreatic beta cells, where it contributes to the hyaluronan matrix around the islets (PMID: 22821669). These are observational, early-stage findings. No study has established that carrying one loss-of-function ITIH2 variant directly raises your risk of developing type 2 diabetes. Standard healthy lifestyle measures — regular exercise, a balanced diet, and periodic blood glucose checks — remain the most appropriate response.

Non-alcoholic fatty liver disease — metabolic association (ITIH2-associated)

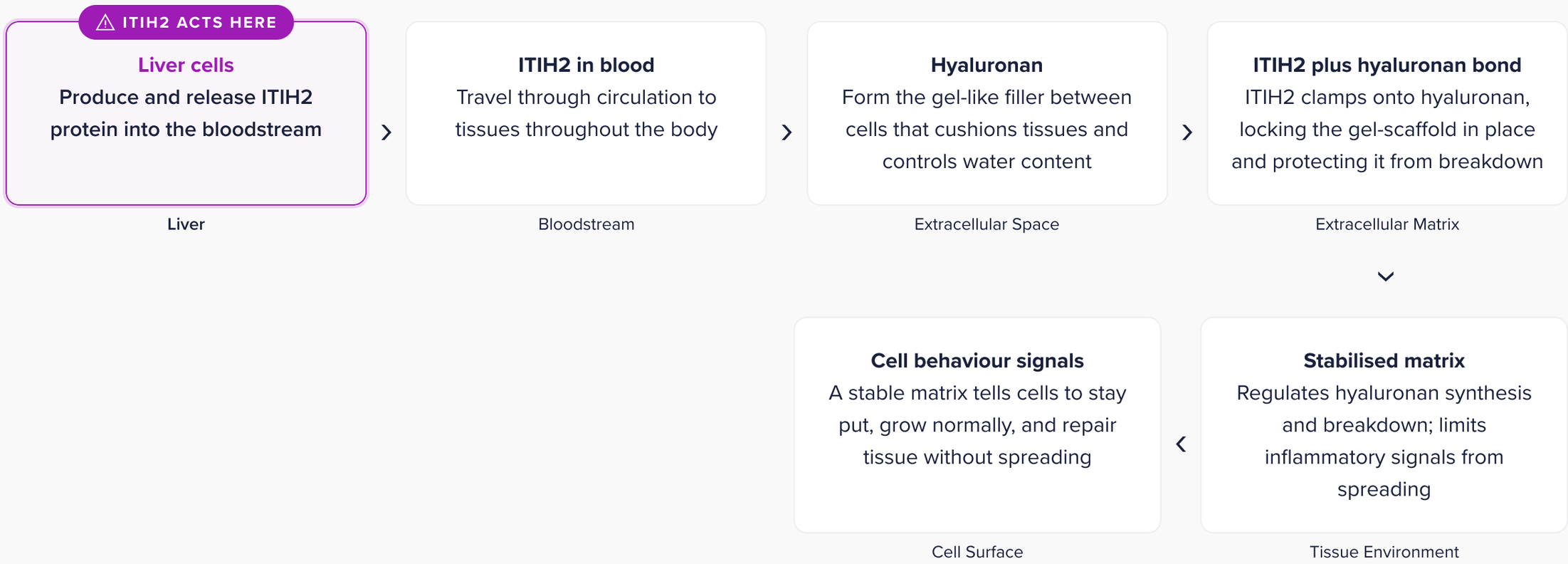
Non-alcoholic fatty liver disease is a condition in which excess fat builds up in liver cells in people who drink little or no alcohol. It can range from simple fat accumulation to more serious inflammation and scarring.

ITIH2 is most strongly expressed in the liver, where it is produced and secreted into the bloodstream. Its appearance in disease association datasets as an NAFLD-linked gene reflects this biological connection, but no published study has demonstrated that a germline loss-of-function variant in ITIH2 causes or substantially worsens non-alcoholic fatty liver disease. This association is currently hypothesis-generating only. Routine liver health monitoring through your primary care provider, along with avoidance of excess alcohol and processed fats, is sensible for everyone.

EXTRACELLULAR MATRIX SCAFFOLDING VIA HYALURONAN ANCHORING

Why this matters: This pathway shows how your body maintains the gel-like cushion between cells, controls inflammation, and keeps tissue architecture intact. ITIH2 is the key fastener in this system, and understanding it explains why its loss is so frequently observed in cancers.

Think of the space between your cells as a jelly-like cushion. Hyaluronan is the main ingredient of that jelly, and ITIH2 acts like a clamp that locks hyaluronan in place and controls how much of it is made or broken down. When the clamp is weaker, the jelly can become disorganised, which can fuel inflammation and make it easier for abnormal cells to move around.



When this pathway is impaired:

With less functional ITIH2, the hyaluronan scaffold is less well anchored, potentially allowing more tissue inflammation and reduced restraint on abnormal cell movement.

KEY ACTIONS

Mention this variant to your primary care doctor so it is noted in your record. Prioritise standard cancer screening for your age, including colorectal cancer screening starting at 45 or earlier if family history warrants it. Keep metabolic health in check with routine blood sugar monitoring given the observational metabolic associations. If you have a family history of early-onset dementia, raise this variant with a genetic counsellor. No specific triggers or things to avoid have been documented for this variant.

OR2T11

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Smell detection	IMPACTFUL	1-248576305-248647941-C-<DEL>-CNV	NP_001001964.1	N/<DEL>	High Impact

OR2T11 is a sensory receptor in your nose, specialized for detecting certain sulfur-based odor molecules. Its most notable job is recognizing the odorant deliberately added to odorless natural gas so people can smell a leak. You have one copy of this gene deleted, while your other copy remains intact. This gene has no established connection to any systemic disease, cancer, or organ condition, and no medical monitoring or treatment is indicated based on current evidence.

GENE EXPRESSION

Most active in: Pancreas · Kidney · Liver · Lung · Colon

WHAT THIS MEANS FOR YOU

One of your two copies of OR2T11 has been deleted. This receptor normally detects the sulfur-based odorants added to natural gas and propane as a safety signal. Your remaining copy is intact and still produces working receptor protein, so there are no health consequences or clinical syndrome linked to this finding. The one practical point is that you may need a slightly higher concentration of these odors to notice them, meaning a faint gas leak could be harder to detect. This is a sensory quirk, not a disease, and simple home safety devices fully compensate for it.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Olfactory receptor loss-of-function (OR2T11, heterozygous deletion)

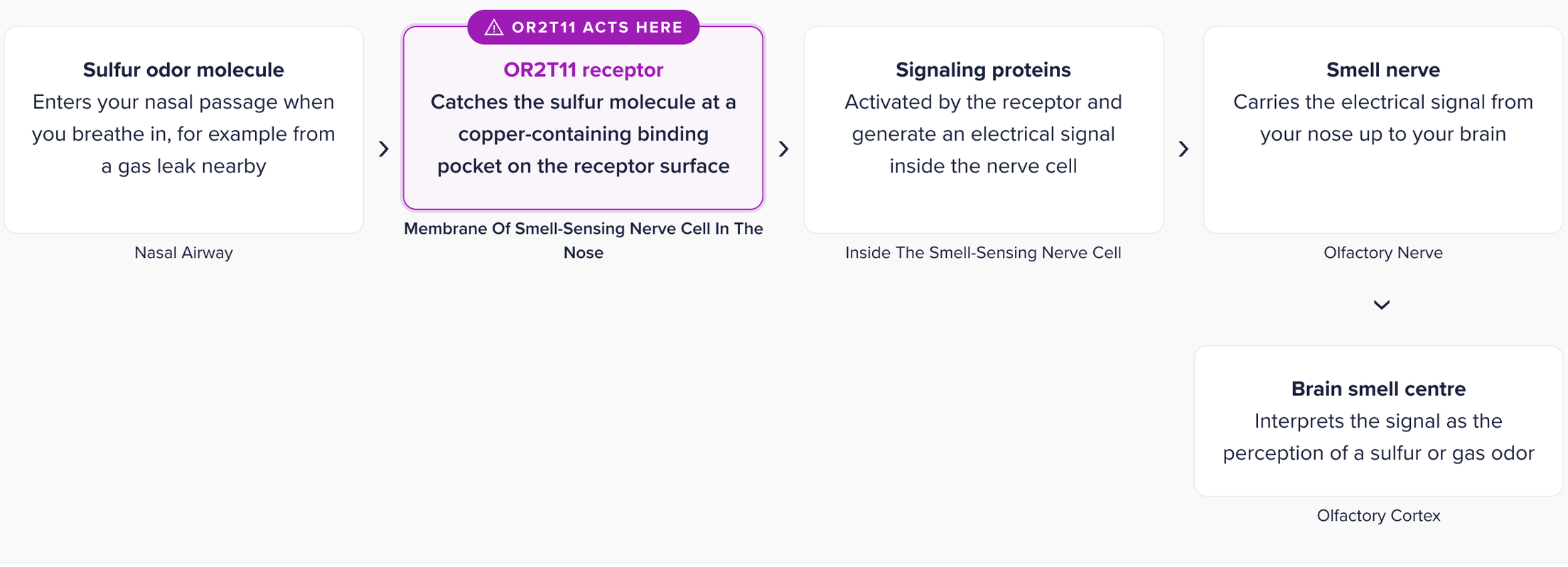
Loss-of-function of olfactory receptors refers to reduced ability to detect specific odor molecules. OR2T11 is responsible for sensing sulfur-based compounds, including the odorants deliberately added to natural gas and propane as safety warnings. When the gene does not produce a full complement of receptor protein, the detection threshold for those specific odors may be elevated, meaning a higher concentration of the smell is needed before the brain registers it.

You carry one deleted copy of OR2T11 alongside one intact, working copy. Because this gene follows an autosomal recessive pattern, your single working copy continues to produce functional receptor protein. The reviewed literature does not document any clinical disease, symptoms, or health consequences linked to having one deleted copy. The only plausible, biologically grounded effect is a subtle elevation in your detection threshold for certain sulfur-based odors, particularly gas-safety odorants like ethanethiol. This has not been confirmed in a study of people with one copy deleted (PMID: 28471462). As a heterozygous carrier, this finding is most relevant to family planning conversations. If you and a future co-parent both carry a deletion in OR2T11, your children would have a 25% chance of inheriting two non-working copies. Even in that scenario, the only documented consequence would be reduced sensitivity to specific sulfur odors, not a serious medical condition.

SULFUR ODOR DETECTION

Why this matters: This pathway shows how your nose normally detects the sulfur-based smell added to natural gas for safety, the most practically relevant consequence of reduced OR2T11 availability.

Think of OR2T11 as a specialized lock on the surface of a smell-sensing cell in your nose. Sulfur odor molecules are the matching key. When enough keys find a lock, a signal fires up to your brain and you perceive the smell. With fewer locks present, you may need a stronger concentration of the odor before the signal reaches your brain.



When this pathway is impaired:

With one copy of OR2T11 deleted, fewer receptor locks are present, so a higher concentration of the sulfur odor may be needed before your brain registers the smell.

KEY ACTIONS

Install carbon monoxide and natural gas detectors on every floor of your home, especially near gas appliances. These devices do not rely on your sense of smell at all. Test them monthly and replace batteries twice a year. If you ever suspect a gas leak, do not rely solely on smell to rule it out: leave the building and call your gas provider from outside. Ensure good ventilation when using gas appliances. No medical referral, medication, or dietary change is needed for this variant.

SLC22A14

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Sperm energy transport	IMPACTFUL	rs138257211	NP_00130696 2.1:p.Leu238Se rfsTer25	ATTTG/A	High Impact

VARIANT POPULATION FREQUENCY: 4/100

SLC22A14 is a transporter in the inner membrane of sperm cell mitochondria. Its job is to pull riboflavin (vitamin B2) inside, where it powers the enzymes that generate the energy driving the sperm tail. You carry one altered copy and one working copy. The altered copy produces a truncated, non-functional protein. All clear evidence of infertility involves losing both copies; no confirmed clinical problem is documented in people with one altered copy. This variant is most relevant if family planning is on your horizon.

GENE EXPRESSION

Most active in: Testis Kidney Colon Lung Liver

WHAT THIS MEANS FOR YOU

You carry one altered copy of SLC22A14, a gene that acts as a doorway letting riboflavin into the energy-generating compartment of sperm cells. With one working copy still active, the evidence does not point to any confirmed health problem for you personally. All well-documented effects come from animal studies where both copies were absent. A human study found lower SLC22A14 protein in men with poor sperm motility, but did not examine men with just one altered copy. Population data suggest single-copy loss is well tolerated. The area most worth noting, if starting a family matters to you, is sperm function. If your partner also carries a SLC22A14 variant, a child could inherit two non-working copies, when more serious effects become plausible.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Spermatogenic failure 65

Spermatogenic failure is a condition in which the testes do not produce sperm that function normally, leading to reduced or absent fertility in males. In the form linked to SLC22A14, the core problem is that sperm cannot generate enough energy to move properly, because the mitochondrial riboflavin transporter needed to fuel the sperm's engine is absent or non-functional.

You have one working copy and one frameshift-altered copy of SLC22A14. All of the mechanistic evidence, including mouse knockout studies showing severely immotile sperm and failed fertilisation, comes from animals where both copies were completely non-functional (PMID: 33882315, PMID: 27811987, PMID: 34704967). The gene's population tolerance score (LOEUF 1.17, pLI near zero) suggests that having one altered copy is well-tolerated across many people. No study has described confirmed fertility problems in men with a single loss-of-function copy. That said, a human case-control study did find lower SLC22A14 protein overall in men with unexplained poor sperm motility (PMID: 29726644), and because the evidence is incomplete rather than reassuring, a semen analysis is the most direct and practical way to know whether your sperm motility is normal. If you are planning to have children and a semen analysis shows any concern, mentioning this variant to a reproductive urologist or fertility specialist would be worthwhile. Because this is an autosomal recessive condition, a concern for your children would arise only if your partner also carried a loss-of-function variant in SLC22A14. A genetic counsellor can help you decide whether partner testing makes sense.

Azoospermia

Azoospermia is the complete absence of sperm in the ejaculate, which is one of the more severe presentations of male infertility. It can arise from problems in sperm production, maturation, or transport out of the reproductive tract.

SLC22A14 appears in genetic association data for azoospermia, but with a low association score (0.09 on OpenTargets), reflecting a weak and not yet confirmed link. All direct experimental evidence involves complete gene knockout in animals, not single-copy loss. There is no published case series or cohort study documenting azoospermia in men heterozygous for an SLC22A14 loss-of-function variant. If you have any concerns about your fertility, a semen analysis is the appropriate first step.

Neurodegenerative disease

Neurodegenerative diseases are conditions in which nerve cells in the brain or peripheral nervous system progressively lose function over time. They typically present with cognitive, motor, or sensory decline, with Alzheimer's disease being the most common example.

SLC22A14 was flagged as a possible candidate locus in a single exploratory GWAS for late-onset Alzheimer's disease (PMID: 29027019). The authors explicitly described this as preliminary and called for further research before drawing conclusions. The variant nominated in that study is not the same as yours, and this gene association has not been validated in subsequent large-scale studies. No biological mechanism linking SLC22A14 to neurodegeneration has been established. This finding does not currently warrant any change to your health monitoring beyond what is standard for your age.

THE RIBOFLAVIN-TO-SPERM-ENERGY PATHWAY

Why this matters: SLC22A14's entire documented biological role is to fuel this pathway. Without riboflavin getting into the sperm's power plant, the enzymes that burn fat and generate movement energy lose the tools they need to work.

Think of a sperm cell's midpiece as a tiny car engine. The engine burns fatty fuel to make the energy that drives the tail. Riboflavin (vitamin B2) is the raw material for the spark-plug components those burning enzymes depend on. SLC22A14 is the door that lets riboflavin into the engine room. When the door does not open, the spark tools cannot be made, the engine misfires, and the sperm cannot swim or activate to reach an egg.

Riboflavin (vitamin B2)
Arrives at the sperm cell, ready to enter the mitochondria

Outside The Mitochondrial Inner Membrane

›

⚠ SLC22A14 ACTS HERE

SLC22A14 transporter
Acts as a doorway, actively pulling riboflavin across the mitochondrial inner membrane into the power plant

Inner Mitochondrial Membrane, Sperm Midpiece

›

FAD and FMN cofactors
Riboflavin is converted into two active helper molecules, FAD and FMN, that plug into energy-making enzymes like spark plugs

Mitochondrial Interior

›

Fat-burning enzymes
FAD powers the enzymes that break down fatty acids, releasing stored chemical energy

Mitochondrial Interior

⌄

TCA cycle
Broken-down fatty acid pieces enter the TCA cycle, which extracts more energy and feeds it into the ATP-generation chain

Mitochondrial Interior

‹

ATP (energy currency)
The energy chain converts all that captured energy into ATP, the molecule that powers the sperm tail

Mitochondrial Inner Membrane

‹

Sperm tail and capacitation
ATP drives the flagellar motor so the sperm can swim and undergo the chemical activation needed to fertilise an egg

Sperm Flagellum And Midpiece

When this pathway is impaired:

When riboflavin cannot enter the mitochondria, fat-burning enzymes lose their cofactors, ATP output drops, and sperm cannot swim or activate properly.

KEY ACTIONS

If starting a family is on your horizon, ask your doctor for a semen analysis. This simple test directly measures sperm motility and will tell you far more than genetics alone can. If motility is low without another explanation, mention this variant to a reproductive medicine specialist. If your partner also carries an SLC22A14 variant, meet with a genetic counsellor before trying to conceive, as a child with two non-working copies could face more serious sperm energy challenges. Keeping riboflavin intake adequate through eggs, dairy, and leafy greens is sensible, though no evidence supports supplementation specifically for your situation.

TLR10

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Immune inflammation control	IMPACTFUL	rs187892716	NP_112218.2:p.Ser245Ter	G/T	High Impact

VARIANT POPULATION FREQUENCY: 2/1,000

TLR10 is your immune system's built-in dimmer switch for inflammation. While most immune receptors raise the alarm when they sense a threat, TLR10 dials the response back down, preventing over-reaction. It is most active in immune cells in your spleen, lungs, and gut. Your variant introduces a premature stop signal that cuts one copy of the protein short. No defined mendelian disease is linked to this gene, so this is a risk-modifier finding rather than a diagnosis of a specific condition.

GENE EXPRESSION

Most active in: Spleen, Colon, Lung, Liver, Kidney

WHAT THIS MEANS FOR YOU

You have one working and one altered copy of TLR10, a gene that brakes your immune system's inflammatory response. With one copy producing a truncated, non-functional protein, that braking is somewhat reduced, though your working copy still contributes. No specific named disease is linked to having one altered copy. Your variant is best understood as a modifier: lower TLR10 activity associates with stronger cytokine responses and, in large population studies, with raised inflammation markers. Over time, a slightly louder inflammatory tone may add a modest nudge toward conditions like asthma or autoimmune susceptibility. Consistent anti-inflammatory lifestyle habits are your most practical tool.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Modulation of Inflammatory Cytokine Response (TLR10 loss-of-function)

TLR10 normally acts as a brake on the innate immune system, dampening the production of pro-inflammatory molecules like IL-1β, TNF-α, and IL-6 after an immune trigger. When this braking function is reduced, the body's inflammatory responses can run stronger and longer than usual after infections or other immune challenges.

You carry one working copy and one copy of TLR10 with a premature stop codon (p.Ser245Ter), which is expected to produce either a truncated, non-functional protein or no protein at all from that copy. Human functional studies show that people with reduced TLR10 activity produce meaningfully higher amounts of IL-1β, TNF-α, and IL-6 in response to immune triggers, in a dose-dependent way (PMID: 25288745). Your working copy still produces functional TLR10, so the braking effect is reduced rather than absent. No named clinical syndrome is caused by having one non-working copy of TLR10, and this variant has no ClinVar entry. This is best understood as a potential modifier of your inflammatory response, not a cause of a specific disease. You may mount somewhat stronger or more prolonged inflammatory responses during infections or other immune challenges, though how much your specific stop-gain variant contributes has not been directly measured.

Asthma and Allergic Airway Disease Susceptibility

Asthma is a chronic condition of the airways involving inflammation, airway narrowing, and hypersensitivity to inhaled triggers. Allergic rhinitis involves a similar immune-driven inflammation of the nasal passages. Both are shaped by the balance between immune activation and regulation in the airways.

TLR10 genetic variation has been associated with asthma risk in human cohort studies, with specific TLR10 variants linked to physician-diagnosed asthma and airway hyperresponsiveness (PMID: 15201134). The gene is expressed in the lung and in B lymphocytes, cell types central to allergic airway disease, and OpenTargets places asthma and allergic rhinitis among the top associations for TLR10 variants (scores 0.49 and 0.38 respectively). Because TLR10 serves as an anti-inflammatory check on early immune responses to inhaled allergens and microbial particles, reduced TLR10 braking from your variant could contribute to a more vigorous airway inflammatory response. The published association studies used common polymorphisms rather than stop-gain variants, so whether your specific variant meaningfully changes your asthma or allergy risk is not yet established. If you experience wheeze, chest tightness, or persistent nasal symptoms, it is worth discussing with your doctor.

Autoimmune Inflammatory Condition Susceptibility (SLE-related and Rheumatoid Arthritis-related)

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are autoimmune conditions driven by an overactive immune response that damages the body's own tissues. SLE primarily affects the skin, joints, kidneys, and other organs; RA primarily causes joint inflammation and erosion.

- **TLR10 expression in B cells was negatively correlated with SLE disease activity across 89 participants, suggesting that lower TLR10 activity is associated with a more active disease state (PMID: 39537946). Separately, a TLR10 variant with impaired NF-κB inhibitory function was associated with more erosive RA disease and poorer response to infliximab in a cohort of over 1,600 patients (PMID: 27716427). These findings are consistent with TLR10's role as an immune brake: when that brake is weaker, autoimmune inflammation can be harder to control. These are population-level associations using different variants, not direct measurements of your specific stop-gain. There is no documentation that having one non-working copy of TLR10 causes SLE or RA. The relevance for you is awareness rather than alarm: if you ever develop joint pain, persistent skin rashes, or unexplained fatigue, it is worth mentioning your TLR10 variant to your doctor as part of the broader picture.**

THE TLR10 INFLAMMATION BRAKE PATHWAY

Why this matters: This pathway shows how TLR10 normally prevents your immune system from over-firing after detecting a threat. Reducing TLR10 activity shifts the balance toward a more reactive inflammatory state, which is the central consequence of your variant.

Think of your immune system as a car engine. TLR2 is the accelerator — it revs up inflammation when it senses bacteria or other dangers. TLR10 is the brake pedal on that same axle, slowing the response down once the danger signal has been received. With less functional TLR10, the brake is less effective, so the engine can run hotter and longer than it would normally.

Microbial signal
A molecular pattern from a microbe or similar trigger arrives at the surface of an immune cell

Outside The Immune Cell

→

TLR2 receptor
TLR2 detects the signal and begins firing an inflammatory alarm inside the cell

Cell Surface Membrane

→

⚠ TLR10 ACTS HERE

TLR10 receptor
TLR10 pairs up with TLR2, forming a joint complex that dials back the alarm signal

Cell Surface Membrane

→

MyD88 adapter
The paired receptors recruit the MyD88 relay protein to pass the calming signal inward

Inner Face Of The Cell Membrane

↓

PI3K/Akt calming signal
TLR10 activates a calming internal signal that steers the cell toward producing anti-inflammatory messengers instead of pro-inflammatory ones

Inside The Cell

←

IL-1Ra messenger
The cell releases IL-1Ra, a molecule that blocks the inflammatory alarm at neighbouring cells

Bloodstream And Tissue

←

NF-κB master switch
With less TLR10 braking, NF-κB stays more active, driving greater production of inflammation chemicals such as IL-1β, IL-6, and TNF-α

Cell Nucleus

When this pathway is impaired:

With reduced TLR10 braking, the immune response can run louder and longer than usual after a trigger, potentially raising the baseline level of inflammation in the body.

KEY ACTIONS

Focus on keeping background inflammation low through consistent daily habits. An anti-inflammatory diet built around vegetables, oily fish, whole grains, and olive oil, while limiting ultra-processed foods, is well supported by evidence. Staying at a healthy weight matters because adipose tissue amplifies inflammatory signalling, and research directly links TLR10 to this pathway. If you have a history of asthma, allergic rhinitis, or recurrent inflammatory symptoms, share this result with your doctor. Mentioning this variant at any future rheumatology or immunology consultation is also worthwhile, given cohort data linking lower TLR10 activity to autoimmune flares.

TRIM32

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Protein recycling	IMPACTFUL	rs199664043	NP_036342.2: p.Arg613Ter	C/T	High Impact

VARIANT POPULATION FREQUENCY: 3/100,000

TRIM32 is your cells' labelling system for worn-out proteins. It tags damaged proteins in muscle, immune, and nerve cells so they can be collected and recycled, keeping muscle fibres healthy. When both copies of this gene stop working, this recycling breaks down and can lead to a slowly progressive muscle-weakening condition called LGMD R8. Because your variant affects only one copy, your other copy continues to run this system. The published evidence strongly supports that one working copy is sufficient to prevent disease in the vast majority of people.

GENE EXPRESSION

Most active in: Spleen | Pancreas | Colon | Lung | Testis

WHAT THIS MEANS FOR YOU

You carry one altered copy of TRIM32 and one fully working copy. Because LGMD R8 is autosomal recessive, your working copy compensates and your personal health risk is low. In a large study of 1000 people investigated for muscle weakness, 26 were in exactly your situation and none developed LGMD R8. This variant matters most for family planning: if your partner also carries a TRIM32 variant, each pregnancy would have a one-in-four chance of inheriting two altered copies, raising a real risk of muscle disease. Knowing this now puts you in a strong position to plan ahead.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

autosomal recessive limb-girdle muscular dystrophy type 2H

Limb-girdle muscular dystrophy type 2H (also called LGMD R8) is a rare inherited muscle disease that causes slowly progressive weakness in the muscles closest to the body's core, particularly the hips, thighs, and shoulders. It typically begins in early to mid-adulthood, progresses slowly, and does not affect the heart or breathing muscles. Mildly elevated creatine kinase is a common laboratory finding.

This condition requires two non-working copies of TRIM32 to develop. You have one altered copy (p.Arg613Ter) paired with one fully working copy. In a study of 1,000 people investigated for muscle weakness, 26 had exactly your situation and none were diagnosed with LGMD R8 (PMID: 29921608). Your personal risk of developing this disease is low. This variant matters most for family planning: if your partner also carries a TRIM32 variant, each pregnancy would have a 1-in-4 chance of inheriting two altered copies and potentially developing the condition.

Bardet-Biedl syndrome 11

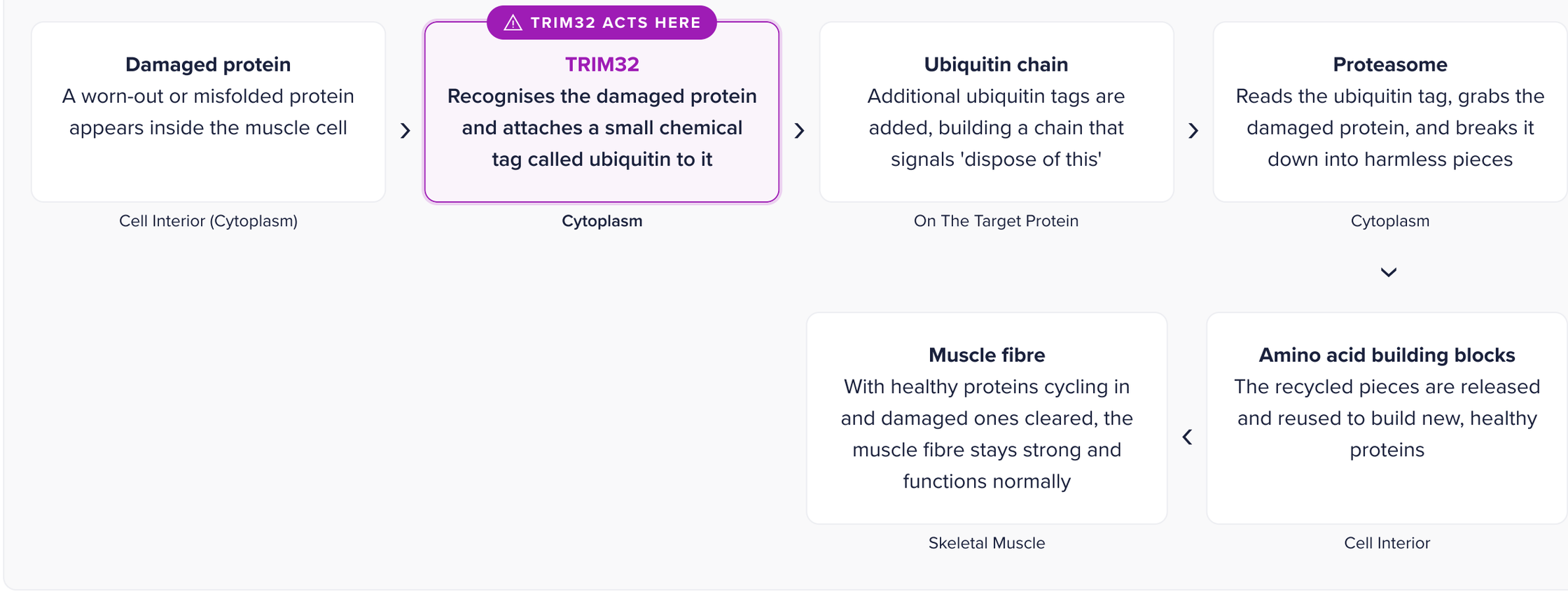
Bardet-Biedl syndrome is a rare inherited multisystem condition that can affect vision (due to retinal degeneration), kidney function, body weight regulation, and development. The BBS11 form is caused by variants in the B-box domain of TRIM32, a region distinct from the NHL-repeat domain where most muscle-disease variants cluster.

Your variant, p.Arg613Ter, introduces a stop signal in the NHL-repeat region of TRIM32, not the B-box domain linked to BBS11. Research confirms that BBS11 arises from B-box domain mutations, while NHL-domain truncations like yours are associated with the muscle disease pathway (PMID: 33802079). There is no established evidence linking NHL-domain heterozygous variants to Bardet-Biedl syndrome. Like LGMD R8, BBS is also autosomal recessive and requires two altered copies to cause disease, so this association is not a personal health concern for you.

THE CELLULAR PROTEIN RECYCLING (UBIQUITIN-PROTEASOME) PATHWAY

Why this matters: TRIM32 is the tagging enzyme at the heart of this pathway in muscle cells. When both copies fail, damaged proteins pile up and muscle fibres age and weaken prematurely, the root mechanism of LGMD R8.

Think of your muscle cells as a busy workshop. Proteins are the tools. Over time, tools wear out. TRIM32 is the worker who spots broken tools and sticks a 'dispose of this' label on them. A recycling machine (the proteasome) then collects labelled tools and breaks them down so parts can be reused. If TRIM32 cannot label broken tools, they pile up and the workshop grinds to a halt.



When this pathway is impaired:

When both copies of TRIM32 fail, the tagging step stalls. Damaged proteins accumulate in muscle fibres, causing progressive weakness (LGMD R8).

KEY ACTIONS

The most important step is discussing this result with a genetic counselor before starting or expanding your family. Your partner can be offered carrier testing for TRIM32 variants. If your partner also carries one, a specialist can walk you through reproductive options including prenatal testing. No monitoring, dietary changes, or medication adjustments are needed for your own health based on current evidence.

AGAP6

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Cell cargo transport	INFORMATIVE	rs575835505	NP_001071133.2:p.Arg70GlyfsTer53	AC/A	High Impact

VARIANT POPULATION FREQUENCY: 13/100

AGAP6 is believed to act as a GTPase-activating protein, a type of molecular switch regulator involved in how cells organise internal transport. Your variant is a frameshift in one of your two copies of this gene. No established germline disease is linked to AGAP6, this variant is not in ClinVar, and population data show people routinely carry similar changes in one copy without apparent harm. The current evidence does not support a recognised clinical syndrome from having one altered copy of this gene.

GENE EXPRESSION

Most active in: Spleen, Liver, Testis, Pancreas, Colon

WHAT THIS MEANS FOR YOU

You carry one altered copy of AGAP6, a gene believed to help regulate your cells' internal sorting and transport system. Your second copy is fully intact, and population data confirm this gene tolerates having one non-working copy quite well. No symptoms, triggers, or health conditions have been linked to one altered copy of AGAP6 in any published research, so this variant is informational rather than a health concern. The main relevance is family planning: if a future partner carried their own AGAP6 loss-of-function variant, each pregnancy would have a one-in-four chance of inheriting two altered copies, though even that scenario has no clearly defined consequence in current literature.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

AGAP6 loss-of-function variant of uncertain significance

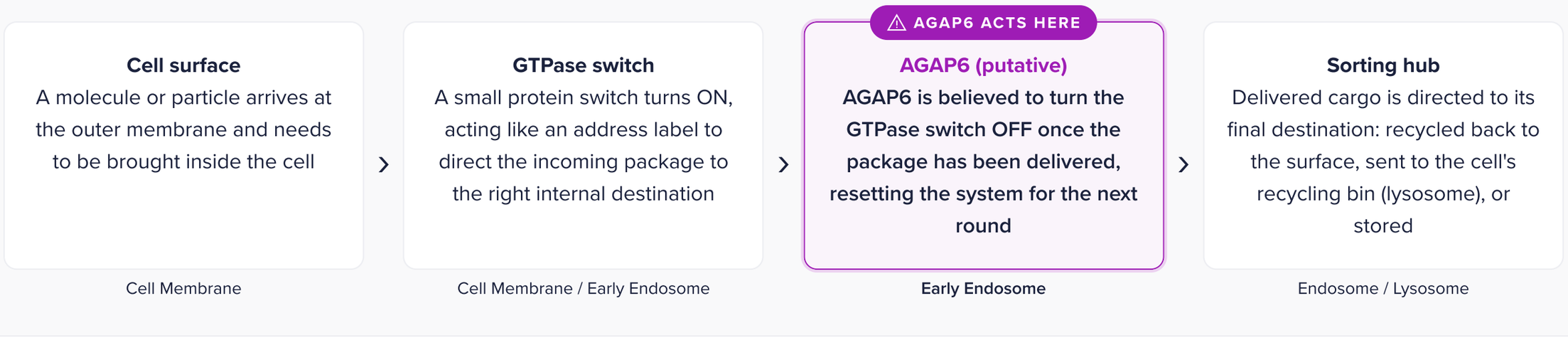
AGAP6 encodes a putative GTPase-activating protein involved in the endocytosis pathway, which governs how cells take in and sort materials internally. Loss-of-function changes reduce or eliminate output from one copy of this gene. No clearly defined clinical syndrome has been established for people with one or two non-working copies of AGAP6.

You carry one frameshift variant (p.Arg70GlyfsTer53) in AGAP6, with your second copy intact and working normally. Because AGAP6 follows autosomal-recessive inheritance and population data show the gene tolerates heterozygous loss-of-function well (LOEUF 0.62, pLI 0.013), no clinical phenotype is expected for you personally. As a heterozygous carrier, your own risk of developing any clinical condition from this variant is low, because your other copy compensates. This variant is most relevant to family planning. If a future partner were also found to carry a loss-of-function variant in AGAP6, each pregnancy would carry a one-in-four chance of a child inheriting two altered copies. Even in that scenario, no clearly defined clinical consequence has been established for biallelic AGAP6 loss. Discussing partner testing with a genetics team is a reasonable step when family planning is on the horizon.

CELL INTERNAL MAIL SORTING (ENDOCYTOSIS)

Why this matters: AGAP6 sits within the endocytosis pathway, which is how cells receive, sort, and recycle molecular cargo from outside. This is the only curated pathway for this gene, making it the central mechanism to understand.

Think of endocytosis as your cell's postal and recycling system. Packages arriving at the cell surface get wrapped up, addressed, and sent to the right internal department. Small protein switches called GTPases act like address labels. They turn on to route a package, then turn off once it arrives. AGAP6 is believed to be one of the helpers that turns those switches off.



When this pathway is impaired:

If AGAP6 cannot reset the GTPase switch, internal cargo routing could be disrupted. This has not been demonstrated in people with one altered copy.

ANKRD36

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Sodium balance	INFORMATIVE	rs141447363	NP_001341516.1 :p.Lys5SerfsTer 29	GC/G	High Impact

VARIANT POPULATION FREQUENCY: 9/100

ANKRD36 produces a protein built around ankyrin repeat domains, which act as molecular clasps helping proteins connect and regulate each other inside cells. Its best-documented role is in the kidney, where it acts as a brake on sodium retention and blood pressure by holding a regulatory protein called YY1 in check. You carry one altered copy alongside one fully working copy. No established Mendelian disease has been linked to having one non-working copy of ANKRD36, and this remains one of the least characterised genes in the human genome.

GENE EXPRESSION

Most active in: Testis, Spleen, Lung, Colon, Pancreas

WHAT THIS MEANS FOR YOU

You have one altered copy of ANKRD36, with your second copy working normally. This gene helps regulate how much sodium your kidneys retain, which influences blood pressure. Research in mice without any working copies showed higher blood pressure on a high-salt diet, and a human study linked lower ANKRD36 activity to essential hypertension. However, no clinical syndrome has been described in people with just one altered copy, as you have. Your working copy compensates, and this finding does not change your medical care today. It is most relevant for family planning: if a future child inherited a similar non-working copy from both parents, discussing this with a genetics specialist at that time would be worthwhile.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Hearing Loss, Autosomal Recessive

Autosomal recessive hearing loss is a form of sensorineural deafness that occurs when both copies of a relevant gene are non-functional. It typically presents from birth or early childhood and affects the inner ear's ability to convert sound into nerve signals.

ANKRD36 appears in disease-association databases with a signal toward autosomal recessive hearing loss (OpenTargets score 0.32), but this link has not been validated in functional studies or clinical cohorts, and no causal mechanism has been established for this gene. Because the inheritance pattern is autosomal recessive, and you have only one altered copy, your working second copy is expected to compensate. There is no evidence that one altered copy on its own causes or meaningfully raises your risk of hearing loss. The more relevant implication is for family planning: if a future biological partner also carried a loss-of-function variant in ANKRD36, each pregnancy would carry a one-in-four chance of a child inheriting two non-working copies, which would be worth discussing with a genetics specialist at that time.

Schizophrenia

Schizophrenia is a complex psychiatric condition affecting perception, thought, and behaviour. It has a strong polygenic component, meaning hundreds of common and rare variants across the genome each contribute a small amount to overall risk.

ANKRD36 carries a database-level association with schizophrenia (OpenTargets score 0.30), but no published functional or clinical study has validated this signal specifically for ANKRD36 loss-of-function variants. No study has demonstrated that having one or two altered copies of ANKRD36 changes schizophrenia risk in humans. This association does not alter any clinical recommendation for you at this time.

Colorectal Cancer

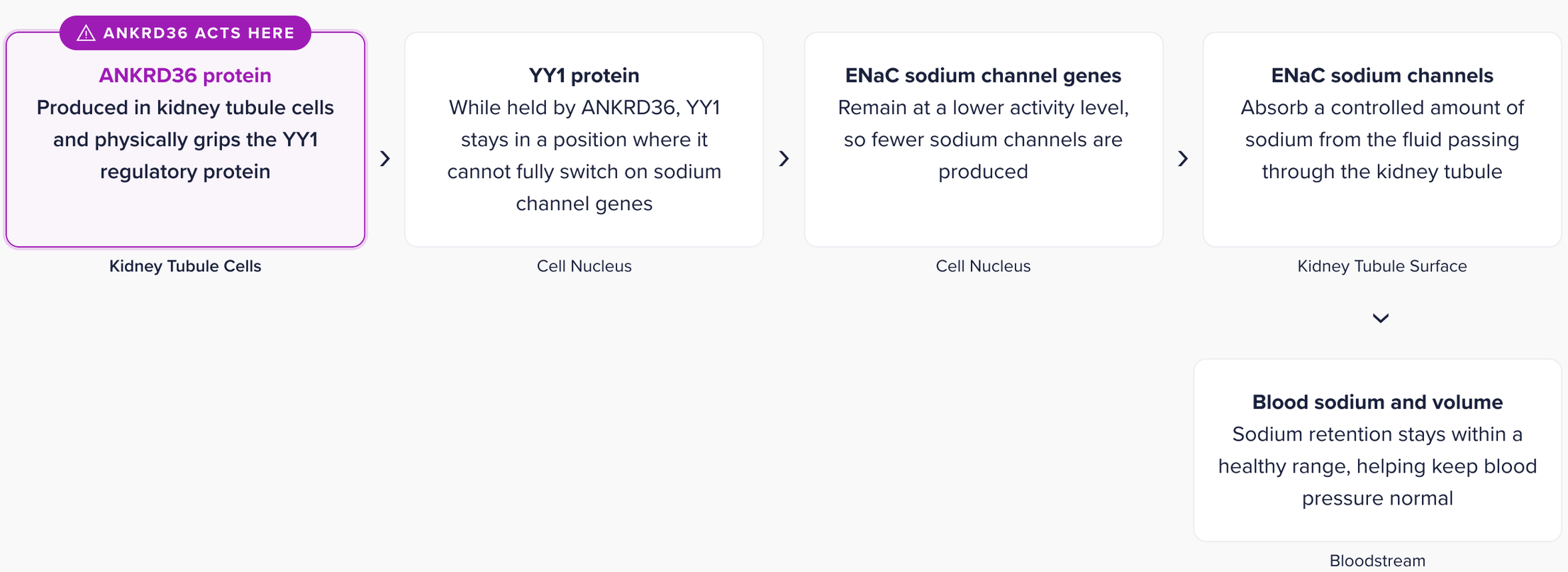
Colorectal cancer arises from abnormal cell growth in the colon or rectum. Most cases are sporadic, though a subset is driven by inherited variants in cancer-predisposition genes. Risk increases with age, family history, diet, and lifestyle factors.

ANKRD36 carries a weak database-level association with colorectal cancer (OpenTargets score 0.11), but there is no published evidence linking ANKRD36 loss-of-function variants to colorectal cancer susceptibility in humans. This signal does not warrant any changes to your colorectal cancer screening beyond what is already recommended for your age and family history. Standard screening guidelines, such as colonoscopy beginning at age 45, or earlier if you have a first-degree family history of colorectal cancer, remain the appropriate guide.

SODIUM BALANCE AND BLOOD PRESSURE REGULATION VIA YY1

Why this matters: The only experimentally validated function of ANKRD36 with mechanistic depth is its role in limiting how much sodium the kidneys retain, directly controlling blood pressure. This pathway is the most clinically relevant for you because reduced ANKRD36 activity has been linked to higher blood pressure in both human cohort data and mouse knockout models.

Think of your kidneys as having tiny salt-retention gates called ENaC channels. How wide those gates open depends partly on a protein called YY1, which acts like a dial controlling how many gates are made. ANKRD36 grabs YY1 and holds it in a position where the salt gates stay relatively closed. When ANKRD36 is less active, YY1 turns the dial up, more salt gates open, the body holds on to more sodium, and blood pressure tends to rise.



When this pathway is impaired:

With less ANKRD36 gripping YY1, the sodium gates are turned up, the body retains more salt, and blood pressure can edge higher.

CCT8L2

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Protein folding	INFORMATIVE	rs139948519	NP_055221.1:p.Trp365Ter	C/T	High Impact

VARIANT POPULATION FREQUENCY: 7/100

CCT8L2 makes a probable molecular chaperone, a protein whose job is to help other newly made proteins fold into the correct three-dimensional shape. It sits in the cytoplasm and is most active in the testis, kidney, and liver. It arose from a gene duplication early in primate evolution and is thought to work alone rather than as part of a larger protein machine. No established disease has been linked to changes in this gene, and your specific variant has not been reported in ClinVar.

GENE EXPRESSION

Most active in: Testis | Colon | Lung | Liver | Kidney

WHAT THIS MEANS FOR YOU

You have one altered copy of CCT8L2, a gene that produces a molecular chaperone — a helper protein that guides newly made proteins into the correct shape. Because CCT8L2 follows an autosomal recessive pattern, your second, fully working copy is expected to compensate. No published study has linked having one non-working copy to any health condition, and there are no known triggers or symptoms to watch for. In practical terms, this result does not change how you should live your day-to-day life. It is most relevant for family planning: if a future partner also carries a loss-of-function variant in CCT8L2, each pregnancy would have a one-in-four chance of inheriting two non-working copies, worth discussing with a genetic counselor.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

CCT8L2-related protein folding alteration (variant of uncertain significance)

CCT8L2 encodes a probable molecular chaperone that helps newly made proteins fold into their correct three-dimensional shapes using ATP energy. It is most highly expressed in the testis and sits in the cytoplasm, where it acts as a standalone folding guide rather than as part of a large multi-protein complex.

You carry one altered copy and one working copy of CCT8L2. Because this gene follows an autosomal recessive pattern, your single working copy is expected to compensate. No clinical condition has been described in people who carry one non-working copy of CCT8L2, and this variant cannot currently be linked to any named Mendelian disease. This finding matters most for family planning: if a future partner also carries a loss-of-function variant in CCT8L2, each pregnancy would have a 1-in-4 chance of inheriting two non-working copies. Even that scenario has no described clinical syndrome in the published literature to date. Gene constraint data are unavailable, so the medical community cannot yet say how sensitive this gene is to dosage changes.

Premature birth (OpenTargets association score 0.18)

Premature birth is defined as delivery before 37 completed weeks of gestation. It is a complex condition driven by many genetic and environmental factors, and no single gene accounts for a large share of risk.

OpenTargets flags a weak statistical association between variants in the CCT8L2 region and premature birth, with a score of 0.18 out of 1.0, indicating a low-confidence signal. This is a population-level observation that has not been validated as a causal relationship. It does not translate into a specific, quantifiable risk for you as a heterozygous carrier, and no clinical guidance exists for this association. You can mention it to a genetic counselor or reproductive medicine specialist if family planning is relevant to you, but it does not require any action on its own.

Scleritis (OpenTargets association score 0.14)

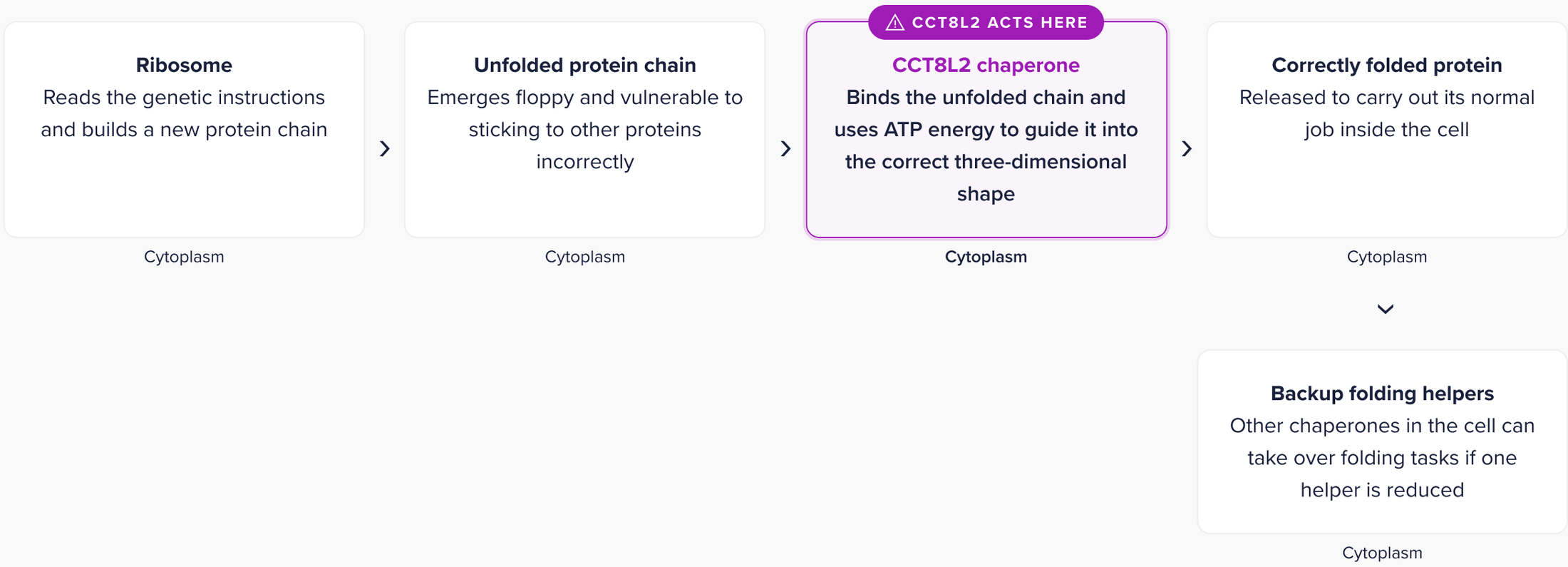
Scleritis is an inflammatory condition affecting the white outer coat of the eye (the sclera). It can cause redness, pain, and in severe cases vision changes, and it is often associated with systemic autoimmune diseases.

OpenTargets reports a very weak statistical signal linking the CCT8L2 region to scleritis, with a score of 0.14 out of 1.0. This is a low-confidence, unvalidated association with no established biological mechanism connecting CCT8L2 to eye inflammation. It does not translate into a specific risk recommendation for you as a heterozygous carrier. If you ever notice persistent eye redness or pain, see an eye doctor as you would for any such symptom, but this variant is not an established reason for extra eye monitoring.

PROTEIN FOLDING QUALITY CONTROL

Why this matters: CCT8L2's known role is helping proteins fold correctly after they are made. This is the only biological process it has been linked to, making it the central pathway to understand for this variant.

Every protein in your body is built as a long chain that must fold into a precise shape to work properly. Chaperones like the one made by CCT8L2 act like folding guides, holding the new chain steady and using energy to coax it into the right shape. Cells have many backup folding helpers, so a reduction in one particular chaperone does not necessarily cause harm on its own.



When this pathway is impaired:

With one altered copy of CCT8L2, the cell may have less of this particular folding guide, but whether that causes a problem has not been shown in any published study.

KEY ACTIONS

Because no heterozygous phenotype has been documented for CCT8L2 and there are no known triggers or symptoms to watch for, there is nothing specific you need to do for your own health based on this finding. If you are planning to have children, it is worth mentioning this result to a genetic counselor so your partner can be offered testing. That conversation is low urgency but genuinely useful for family planning.

DHDH

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Chemical detoxification	INFORMATIVE	rs10423255	NP_055290.1:p.Gln233Ter	C/T	High Impact

VARIANT POPULATION FREQUENCY: 6/100

DHDH holds the instructions for making dihydrodiol dehydrogenase, an enzyme that helps your body neutralise potentially harmful chemicals from the environment and from normal metabolism. It also plays a role in processing certain sugars. The gene is most active in your kidneys, testes, and spleen. You have one working copy alongside one altered copy. No defined inherited condition has been linked to carrying one altered copy of DHDH, and population data show that one non-working copy is well tolerated in healthy people.

GENE EXPRESSION

Most active in: Kidney, Testis, Spleen, Lung, Liver

WHAT THIS MEANS FOR YOU

You have one working copy of DHDH and one with an early stop signal. Your working copy keeps producing functional enzyme that helps convert reactive chemical by-products into forms your body can excrete. No health condition is linked to having one altered copy, and population data confirm this is well tolerated. This result is mainly relevant to family planning: if a future co-parent also carries an altered DHDH copy, there is a 1-in-4 chance per pregnancy of a child inheriting two altered copies. That scenario has not been tied to a defined disease, but a genetics specialist can advise, especially since broad carrier screening is standard for Ashkenazi Jewish background.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Loss-of-function variant in DHDH (xenobiotic detoxification pathway)

DHDH produces dihydrodiol dehydrogenase, an enzyme that converts reactive chemical by-products into water-soluble forms the body can safely remove. It plays a supporting role in the liver, kidneys, and other tissues as part of the broader xenobiotic detoxification system. No Mendelian disease has been linked specifically to changes in this gene.

You have one working copy of DHDH and one copy carrying an early stop signal (p.Gln233Ter). Your working copy continues to produce functional enzyme, and the gene's population constraint score (LOEUF roughly 1.19) tells us that one non-working copy is common in healthy people and well tolerated. No clinical symptoms or health condition have been documented in people who carry one altered DHDH copy. Because DHDH follows an autosomal recessive inheritance pattern, you are a carrier whose own health is not expected to be affected. This is most relevant to family planning: if a future co-parent also carried an altered DHDH copy, each pregnancy would have a 1-in-4 chance of inheriting two altered copies. Even that scenario has not been tied to a defined disease so far, but it is worth discussing with a genetics specialist. Expanded carrier screening across a broad gene panel is also standard practice for people of Ashkenazi Jewish background, so this is a good conversation to have with your doctor if you have not had that screening already.

Prostate cancer (OpenTargets association, score 0.11)

Prostate cancer arises from uncontrolled growth of cells in the prostate gland and is the most common solid cancer in men. Inherited genetic factors can influence lifetime risk, though most cases reflect a combination of common variants, lifestyle, and age.

DHDH appears in an OpenTargets prostate cancer association with a very weak score of 0.11 out of 1.0. This is a statistical signal from large databases, not a validated causal gene-disease relationship, and no study has shown that carrying one altered DHDH copy meaningfully raises prostate cancer risk. Standard age-appropriate prostate health discussions with your doctor remain appropriate, but this variant does not currently justify additional surveillance beyond what would be recommended for any 37-year-old man.

THE CHEMICAL CLEAN-UP PATHWAY (XENOBIOTIC DETOXIFICATION)

Why this matters: This is the pathway through which your body recognises, processes, and removes potentially harmful chemicals. DHDH contributes one specific step — converting reactive chemical by-products into water-soluble forms — making it the central process to understand for this variant.

Think of this pathway as a multi-step waste disposal system inside your cells. When harmful chemicals enter your body from the environment, certain foods, or everyday metabolism, a sequence of enzymes works together to make those chemicals harmless and ready for removal. DHDH handles a specific reactive by-product called a dihydrodiol, converting it into a form the kidneys can clear through urine.

Harmful chemical
An environmental or metabolic chemical enters a cell in the kidney, liver, or other tissue.

Inside The Cell

›

Cytochrome P450 enzymes
First-responder enzymes begin chemically modifying the harmful substance to make it more reactive and easier for later enzymes to act on.

Cell Membrane Structures

›

Reactive intermediate
The modified chemical becomes a reactive intermediate compound called a dihydrodiol, which can cause cellular damage if left unprocessed.

Cell Fluid

›

⚠ DHDH ACTS HERE

DHDH enzyme
Dihydrodiol dehydrogenase converts the reactive intermediate into a safer, water-soluble compound, defusing its harmful potential.

Cell Fluid

⌄

‹

Water-soluble waste product
The now-harmless compound is packaged for transport out of the cell.

Cell Fluid

Kidney filtration
The waste compound travels to the kidneys, is filtered from the blood into urine, and is cleared from the body.

Kidney

When this pathway is impaired:

With one altered copy, the DHDH clean-up step runs with reduced enzyme. The rest of the pathway remains intact, and no clinical disease from this reduced capacity has been documented in people with one working copy.

FLG2

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Skin barrier protection	INFORMATIVE	rs556285121	NP_001014364.1:p.Gln1034ProfsTer192	GTATT/G	High Impact

VARIANT POPULATION FREQUENCY: 1/1,000

FLG2 makes filaggrin-2, a protein in the outermost skin layers that glues cornified cells together, locks in moisture, and releases antimicrobial fragments to fight surface bacteria. You have one altered copy and one working copy. The serious condition tied to FLG2 loss, peeling skin syndrome type A, only occurs with two non-working copies. With one working copy active, your risk of that condition is expected to be very low. Whether one altered copy modestly affects everyday skin resilience is not yet established.

GENE EXPRESSION

Most active in: Testis | Pancreas | Colon | Lung | Liver

WHAT THIS MEANS FOR YOU

You carry one altered copy of FLG2, the gene that instructs skin cells to make filaggrin-2, a protein that helps hold the outer skin layer together, seals in moisture, and supports the skin's natural defences. With one working copy still active, your skin continues to produce filaggrin-2. The severe skin-peeling condition linked to this gene requires two non-working copies and has only been seen in consanguineous families, so you are not expected to develop it. Whether a single altered copy modestly nudges the chance of dry skin or eczema is uncertain. Inflammation and environment shape filaggrin-2 levels as much as genetics does. This result is most relevant for family planning rather than your day-to-day health.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

peeling skin syndrome 6

Peeling skin syndrome type A (also catalogued as peeling skin syndrome 6) is a rare inherited skin disorder in which the outermost layers of skin spontaneously detach, producing painless but persistent peeling. It is caused by loss of the proteins that glue the cornified skin cells together, and symptoms are typically worsened by heat and friction.

- **This condition is autosomal recessive, meaning it requires two non-working copies of FLG2 to develop. You carry one altered copy and one fully working copy. Every reported family with this syndrome had two non-working copies, all from consanguineous (closely related) families (PMID: 29758285). With your working copy still producing functional filaggrin-2, you are not expected to develop this condition yourself. This variant is most relevant for family planning: if a future child inherits a second FLG2 loss-of-function variant from their other parent, that child could be affected. A genetic counsellor can help you think through what that means practically.**

atopic eczema

Atopic eczema (atopic dermatitis) is a common chronic inflammatory skin condition marked by dry, itchy, and inflamed skin. It arises from a combination of a weakened skin barrier and an overactive immune response, and it often runs alongside allergies and asthma.

- **FLG2 is one of several proteins that keep the skin barrier intact and naturally moisturised. Research shows FLG2 levels drop in inflamed eczema skin, driven partly by inflammatory signals (interleukins IL-4, IL-13, IL-25) rather than genetics alone (PMID: 23403047). At the gene level, FLG2 loss-of-function mutations have been linked to more persistent eczema symptoms in some cohorts (PMID: 24184149), though that study focused on different variants in African American children, so it does not directly measure your specific variant's contribution. Whether your single altered copy meaningfully raises your personal risk above the general population has not been established in the reviewed literature. If you already experience eczema, it is worth mentioning this variant to your dermatologist, as it adds useful context about your skin barrier biology.**

peeling skin syndrome

Peeling skin syndrome is a broad group of rare genetic skin disorders defined by spontaneous or trauma-induced shedding of the skin's outer layers. Subtypes vary in severity, extent, and associated inflammation, and all share a defect in the adhesion proteins that hold cornified skin cells together.

As with peeling skin syndrome 6 above, all documented cases caused by FLG2 have involved two non-working copies (PMID: 29758285). You have one working copy, so this broader category of the condition is not expected to affect you directly. The relevance here is the same as for the other subtypes: family planning considerations if your partner also carries an FLG2 loss-of-function variant.

peeling skin syndrome type A

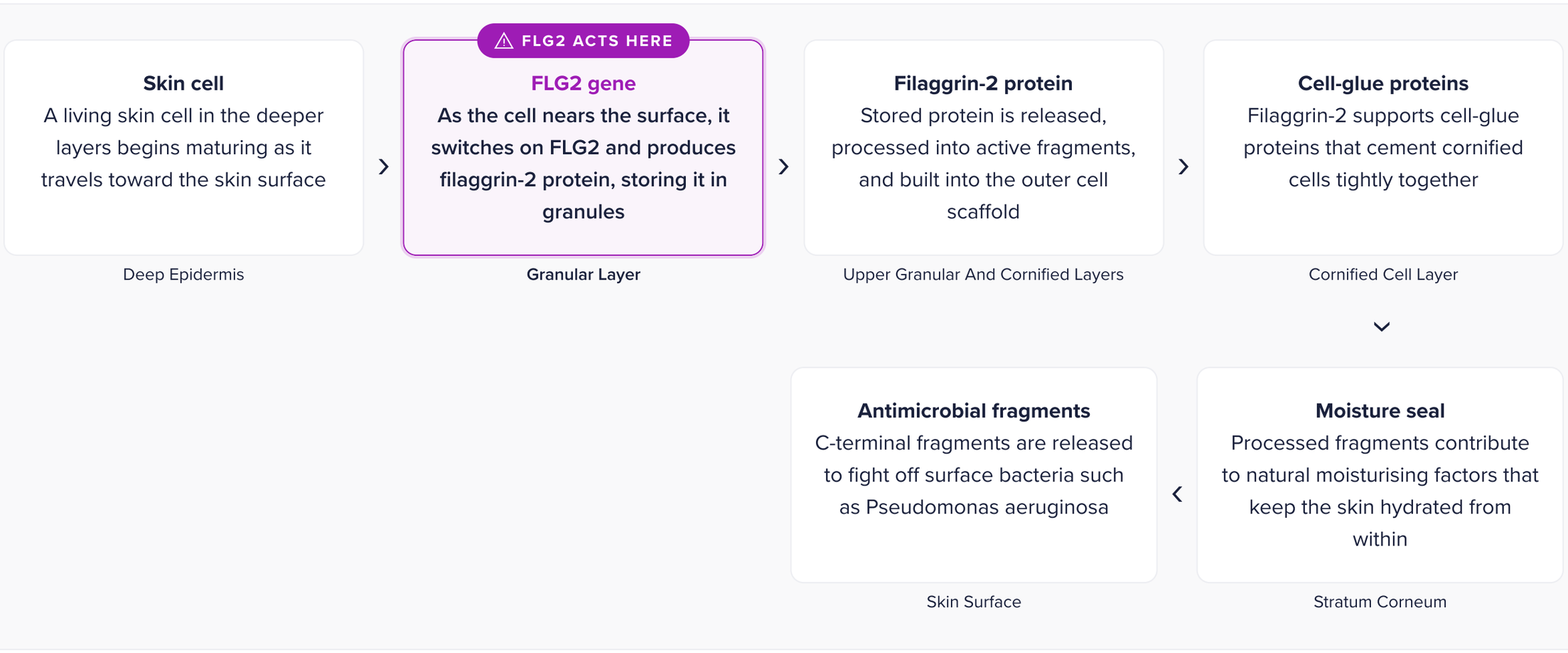
Peeling skin syndrome type A is the non-inflammatory subtype of peeling skin syndrome, characterised by painless, generalised superficial skin peeling that worsens in warm temperatures and with physical friction. It is the specific subtype directly caused by biallelic FLG2 loss-of-function.

This is the condition most directly tied to FLG2. All documented cases required two non-working copies of the gene, all within consanguineous families (PMID: 29758285). You have one working copy, so you are not at risk of developing this condition yourself. As a heterozygous carrier of one altered copy, you could pass this variant to your children, which becomes relevant only if their other parent also carries an FLG2 loss-of-function variant.

CORNIFIED ENVELOPE FORMATION

Why this matters: This is the process by which skin cells in the outermost layer transform into the tough, water-retaining, germ-repelling shield that protects the whole body. Filaggrin-2 is a structural component of this process, specifically in the steps that glue cells together and lock in moisture.

Think of your skin's outer layer as a brick wall: skin cells are the bricks, and proteins like filaggrin-2 act as mortar and waterproof sealant. When filaggrin-2 is reduced, the wall can become slightly looser, letting moisture escape and making it easier for irritants to get in. In your case, one of your two sets of instructions for making this mortar is disrupted, while the other copy continues working.



When this pathway is impaired:

When both copies are lost, the mortar is almost entirely absent and skin layers peel apart. With one altered copy, filaggrin-2 production is reduced, but the clinical impact is not yet established.

KEY ACTIONS

There are no specific medical interventions required based on current evidence. The most meaningful step is to speak with a genetic counsellor if you are planning to have children, since peeling skin syndrome type A requires two non-working copies of FLG2. A counsellor can help you decide whether partner testing makes sense. Good general skin-care habits, such as a gentle moisturiser and mild soaps, are reasonable regardless of this result.

GSDMC

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Cell death signaling	INFORMATIVE	rs16904150	Altered protein assembly	C/T	High Impact

VARIANT POPULATION FREQUENCY: 7/100

GSDMC produces Gasdermin C, a cellular "demolition" protein. Its job is to help damaged or abnormal cells self-destruct through pyroptosis, sending inflammatory alarm signals to the immune system. You have one working copy and one altered copy. No established single-gene disease is linked to this situation. The chromosomal region around GSDMC shows population-level links to back pain and spinal conditions in large studies, though that connection has not been proven to be caused by GSDMC specifically.

GENE EXPRESSION

Most active in: Spleen Lung Kidney Liver Colon

WHAT THIS MEANS FOR YOU

You have one altered copy of GSDMC, a gene that makes a protein involved in a controlled form of cell death called pyroptosis. Think of Gasdermin C as an alarm system: it stays silent until a specific trigger fires, then punches tiny holes in the cell wall to alert nearby immune cells. Your gene constraint score suggests GSDMC tolerates this kind of variation well across the population, and no recognised clinical condition is linked to having one altered copy. Large studies have noted a statistical link between the GSDMC region and chronic back pain or lumbar spinal stenosis, but that signal has not been traced to a specific loss-of-function variant, and no guidelines exist. This finding is informational for now.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Back pain (chronic) — GWAS association near CCDC26/GSDMC

Chronic back pain is persistent pain in the back lasting three months or more. It is one of the leading causes of disability worldwide and arises from a complex mix of structural, inflammatory, and genetic factors affecting the spine and surrounding tissues.

A large genetic study of over 158,000 people found that a region of DNA near GSDMC was statistically linked to chronic back pain, with a small effect of about 5% higher odds (PMID: 30261039). This is a population-level signal from a broad chromosomal neighbourhood, not evidence that a specific loss-of-function change in GSDMC itself causes back pain. Your variant has not been directly tested in this context, and no clinical management guideline exists for this association. Staying physically active, maintaining a healthy weight, and discussing any persistent back symptoms with your doctor is the most evidence-backed approach for anyone, regardless of this finding.

Lumbar spinal stenosis — GWAS association near GSDMC

Lumbar spinal stenosis is a narrowing of the spinal canal in the lower back that can compress the nerves travelling through it, sometimes causing pain, numbness, or weakness in the legs, particularly with prolonged standing or walking.

A genetic study of around 800 participants found variants near GSDMC more often in people with lumbar spinal stenosis, and higher GSDMC expression was observed in tissue from affected patients (PMID: 33273635). As with the chronic back pain signal, this is a regional genomic association rather than evidence that your specific variant directly causes spinal stenosis. No clinical surveillance protocol has been established based on this finding. If you develop leg pain, numbness, or weakness when walking that is relieved by sitting, that is always worth discussing with your doctor, not because of this variant specifically, but because those symptoms deserve evaluation on their own.

THE CELL SELF-DESTRUCT SIGNAL PATHWAY (PYROPTOSIS VIA GASDERMIN C)

Why this matters: This pathway explains how your body tells individual damaged or stressed cells to sacrifice themselves by punching holes in their own outer wall to alert the immune system. Your variant affects the protein that physically carries out the final hole-drilling step.

Think of Gasdermin C as a controlled explosive charge inside each cell. Most of the time it is completely inert. Only when a specific molecular trigger fires, the enzyme caspase-8, does it get armed and drill holes in the cell wall, causing the cell to burst open and send an alarm signal to nearby immune cells. With one altered copy of GSDMC, the charge may be harder to arm in some situations.

Cell stress signal
A cell detects a problem such as infection, low oxygen, chemical damage, or an immune signal like TNF

Cell Surface And Interior

›

Caspase-8 enzyme
The stress signal activates a cutting enzyme called caspase-8 inside the cell

Cytoplasm

›

⚠ GSDMC ACTS HERE

Gasdermin C (GSDMC)
Caspase-8 cuts the Gasdermin C protein, separating its active front piece from its inactive back piece

Cytoplasm

›

Active Gasdermin C fragment
The freed front piece travels to the cell's outer wall and inserts itself, drilling small pores through the membrane

Cell Membrane

⌄

Pores in cell wall
The holes let water and inflammatory alarm molecules flow in and out, causing the cell to swell and burst open

Cell Membrane

‹

Immune alarm signal
The burst cell releases inflammatory signals that recruit immune cells to clean up the damage and fight any infection

Surrounding Tissue

When this pathway is impaired:

With reduced Gasdermin C, the protein that drills the exit holes may be less available, meaning some stressed cells may not trigger the full alarm response as effectively.

GSTA4

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Cell detoxification	INFORMATIVE	rs749259552	NP_001503.1:p.Thr185SerfsTer5	CTG/C	High Impact

VARIANT POPULATION FREQUENCY: 7/100,000

GSTA4 produces an enzyme whose main job is neutralising 4-hydroxynonenal (4-HNE), a toxic byproduct cells generate when burning fat under stress. Think of it as a clean-up crew that tags chemical waste for safe export. You have one working copy and one copy disrupted by your variant. No Mendelian disease is established for a single altered copy, and the gene's tolerance score (LOEUF ~0.95) shows these variants are relatively common in the population without a strong disease signal.

GENE EXPRESSION

Most active in: Lung · Testis · Liver · Kidney · Pancreas

WHAT THIS MEANS FOR YOU

You have one altered copy of GSTA4, the gene that makes an enzyme responsible for neutralising 4-HNE, a toxic byproduct cells produce naturally when burning fat. Think of this enzyme as a clean-up crew that tags harmful molecules so they can be safely removed. With one non-working copy, your crew is somewhat smaller, but your remaining working copy and related enzymes step in to compensate under everyday conditions. No medical condition has been linked to having just one altered copy, and population genetics data confirm the gene tolerates this change without clear harm. Database associations with Parkinson's or Alzheimer's disease reflect research into general enzyme activity, not studies of people with a single altered copy like yours. No clinical management is needed right now.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Neurodegenerative disease (GSTA4-associated, observational)

Neurodegenerative diseases are conditions in which nerve cells progressively deteriorate or die, leading to problems with movement, cognition, or other neurological functions. Conditions in this category include Parkinson disease and Alzheimer disease, both of which have been studied in relation to oxidative stress and lipid peroxidation.

- **Research in rat models of Parkinson disease shows that higher GSTA4 activity protects dopamine-producing neurons from oxidative damage (PMID: 29681884), and database scoring places GSTA4 among genes with observational ties to neurodegenerative conditions. However, these associations come from studies of overall GSTA4 enzyme levels, not from people with one altered copy like yours. No human genetic study has demonstrated that having one non-working copy of GSTA4 raises your risk of developing Parkinson disease, Alzheimer disease, or any other neurodegenerative condition. Your remaining working copy, together with other glutathione S-transferase enzymes, continues to provide meaningful 4-HNE clearance. This is an exploratory research association, not an established clinical risk for you.**

Multiple sclerosis (GSTA4-associated, observational)

Multiple sclerosis is a chronic autoimmune condition in which the immune system attacks the protective myelin sheath around nerve fibres in the brain and spinal cord, disrupting communication between the brain and the rest of the body.

- **Laboratory studies in mouse models of multiple sclerosis show that GSTA4 promotes the survival of myelin-producing cells by suppressing a cell death pathway, and mice with no GSTA4 had impaired remyelination (PMID: 32792491). This is experimental mouse data only. No human genetic evidence links one altered copy of GSTA4 to a higher risk of developing multiple sclerosis. This association is observational and exploratory, not a clinical risk finding for you.**

Lysosomal storage disease (GSTA4-associated, observational)

Lysosomal storage diseases are a group of inherited metabolic disorders caused by the build-up of toxic materials inside the cell's recycling compartments (lysosomes), typically due to enzyme deficiencies. They can affect multiple organ systems.

- **GSTA4 appears in research databases as having an observational association with lysosomal storage disease, likely reflecting the gene's broader role in managing cellular waste products and oxidative stress. There is no established mechanism or human genetic evidence connecting one altered copy of GSTA4 to lysosomal storage disease. This is a low-confidence database association, not a clinical risk finding for you.**

GLUTATHIONE DETOXIFICATION OF LIPID PEROXIDATION BYPRODUCTS

Why this matters: This pathway is how your cells neutralise and remove 4-HNE, a toxic waste product generated every time cells use fat for energy under oxidative stress. When 4-HNE accumulates, it triggers inflammation and programmed cell death, particularly in metabolically active tissues.

Think of 4-HNE as corrosive exhaust your cells produce while burning fat for fuel. Normally, GSTA4 acts like a clean-up crew that sticks a handle (glutathione) onto the toxic molecule so it can be safely carried out of the cell. With one copy of GSTA4 working less efficiently, the crew is somewhat reduced, but related enzymes can often fill in under everyday conditions.

When this pathway is impaired:

Reduced GSTA4 activity means 4-HNE may linger longer inside cells under high oxidative stress, potentially tipping the balance toward inflammation and cell damage.

KLHL35

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Protein recycling	INFORMATIVE	rs756778027	NP_001034637.2:p.Ser68Alafs Ter121	TCGGGCCGCCCGGCCGCGAACAAGCTG/T	High Impact

VARIANT POPULATION FREQUENCY: **7/1,000**

KLHL35 belongs to the Kelch-like protein family, whose members act as adaptors in a cellular quality-control system. The protein normally helps tag unwanted or surplus proteins so the cell can break them down and recycle their parts, keeping the protein balance tidy. Your variant introduces a frameshift that likely produces a shortened, non-functional protein from one copy of the gene. Importantly, no inherited clinical syndrome has been linked to having one altered copy of KLHL35. This is a genuinely uncertain result, not a diagnosis.

GENE EXPRESSION

Most active in: Testis · Pancreas · Spleen · Lung · Kidney

WHAT THIS MEANS FOR YOU

You have one working copy and one altered copy of KLHL35. The altered copy carries a frameshift that almost certainly stops it producing a functional protein. KLHL35 normally acts as a tagging worker in your cell's recycling system, marking specific proteins for removal. With one copy affected, that activity may be reduced in tissues where the gene is most active, especially the testis, pancreas, and spleen. That said, science has not documented any health condition, symptoms, or clear disease risk tied to having one altered copy of this gene. What is known comes from cancer-tissue research, not from people born with this change. Your variant is real and worth keeping on file, but its meaning for daily health is genuinely uncertain today.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Coronary Artery Disease

Coronary artery disease is a condition in which the arteries supplying blood to the heart muscle gradually narrow, usually due to a build-up of fatty plaques. Over time this can reduce blood flow to the heart and raise the risk of heart attack.

Coronary artery disease appears as the top statistical association for the KLHL35 gene region in population genomic databases, with a modest score of 0.33. This figure comes from large population-level analyses across millions of genetic markers, not from studies of people with one loss-of-function copy of KLHL35. No research has shown that a germline heterozygous frameshift in this gene directly causes or meaningfully raises your personal risk of CAD. At 37, following heart-healthy habits such as regular physical activity, a balanced diet, not smoking, and knowing your blood pressure and cholesterol numbers is the right approach for any man your age, and this variant does not change that advice based on current evidence.

Neurodegenerative Disease

Neurodegenerative diseases are a broad group of conditions, including Alzheimer's disease and Parkinson's disease, in which nerve cells progressively lose function or die. This can affect memory, movement, and other aspects of brain health over time.

KLHL35 appeared as a feature gene in a bioinformatics model of an Alzheimer's disease subtype linked to a particular cell-death pathway, but no causal germline connection was established in that work (PMID: 38478169). The neurodegenerative disease association score of 0.30 in population databases reflects a computational signal, not clinical evidence that your variant raises your personal risk. No human genetics study has connected one loss-of-function copy of KLHL35 to any neurodegenerative condition. This association does not currently change any monitoring or lifestyle recommendation for you.

Lichen Planus

Lichen planus is an inflammatory condition that can affect the skin, nails, hair, and mucous membranes. It typically causes itchy, flat-topped, purplish bumps on the skin or lacy white patches inside the mouth.

The association between the KLHL35 gene region and lichen planus carries a very low score of 0.07 in population genomic databases. No study has shown that a germline loss-of-function variant in KLHL35 causes or predisposes to lichen planus, and no mechanism has been proposed. This association does not currently change any recommendation for you.

Abruptio Placentae

Abruptio placentae, also called placental abruption, is an obstetric complication in which the placenta separates prematurely from the uterine wall before delivery. This can deprive the baby of oxygen and nutrients and cause serious maternal bleeding.

Placental abruption is a pregnancy-specific condition that is not relevant to you. The very low association score of 0.03 further underscores that this is a weak and non-applicable statistical signal in your context.

THE PROTEIN RECYCLING TAG SYSTEM

Why this matters: KLHL35's core role is as a 'spotter' in a three-part protein recycling team. Understanding this team explains how losing one functional copy of KLHL35 could reduce the cell's ability to clear specific proteins, even though which proteins those are remains unknown for KLHL35 specifically.

Think of your cell as a busy kitchen. Every so often, expired or surplus ingredients need to be collected and removed so they do not pile up. KLHL35 is like a kitchen worker who spots those specific ingredients, attaches a coloured sticker to them, and hands them to the bin crew. With one less functional worker, some ingredients may not get stickered and cleared on schedule.

Target protein
A specific protein that needs to be cleared builds up inside the cell

Cell Interior

⚠ KLHL35 ACTS HERE

KLHL35 spotter
KLHL35 recognises and grabs the target protein using its Kelch recognition arms

Cell Interior

Cullin3 scaffold
KLHL35 docks onto the Cullin3 scaffold, bringing the target protein into position for labelling

Cell Interior

Ubiquitin tag
The complex attaches a small ubiquitin label to the target protein, marking it for disposal

Cell Interior

Proteasome shredder
The labelled protein is recognised and broken down into harmless pieces that the cell can reuse

Cell Interior

When this pathway is impaired:

With reduced KLHL35 activity, the specific proteins it normally spots may not get labelled and cleared efficiently, potentially building up inside cells.

MFSD4B

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Nutrient transport	INFORMATIVE	rs117505745	NP_699200.2: p.Leu182Ter	T|A	High Impact

VARIANT POPULATION FREQUENCY: 3/100

MFSD4B makes a transporter protein on the outer surface of cells in your kidney, liver, and testis. It uses the natural inward flow of sodium to pull glucose into cells for fuel, and in the kidney it also helps urea move through to concentrate urine. Your variant creates a premature stop signal predicted to shorten the protein. Despite being a significant-looking molecular change, no human disease has been linked to MFSD4B loss of function in the reviewed literature, so what this means for your health is genuinely unknown at this time.

GENE EXPRESSION

Most active in: Testis | Kidney | Liver | Spleen | Lung

WHAT THIS MEANS FOR YOU

You carry one copy of a stop-gain variant in MFSD4B, a gene encoding a transporter that uses sodium to pull glucose into cells and helps regulate urea in the kidney. Your second, working copy continues to produce full-length protein, so this transport route is not fully lost. No human disease has been confirmed from losing MFSD4B function, and no symptoms are linked to carrying one altered copy. Your health is very likely unaffected. The main relevance is for family planning: if a future partner also carries an altered copy, a genetic counselor can walk you through what that would mean for any children.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

MFSD4B-related loss-of-function (candidate, unconfirmed)

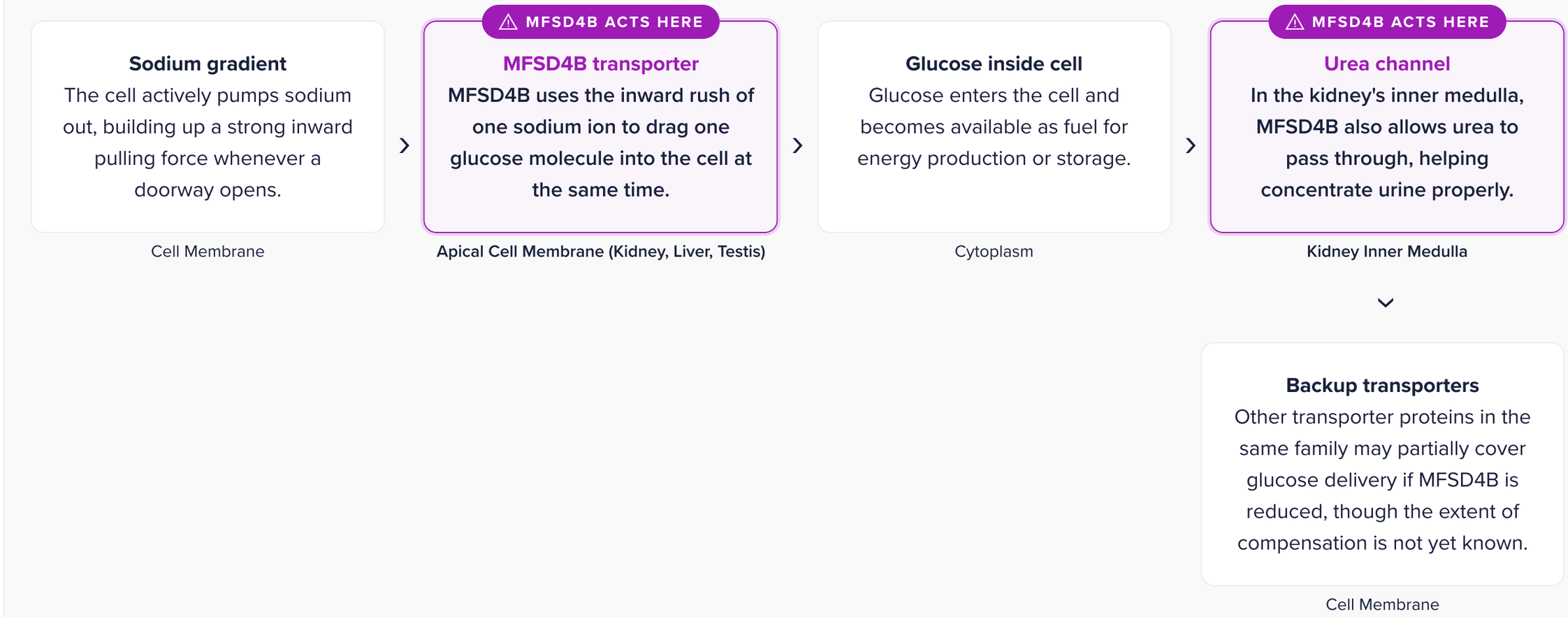
MFSD4B encodes a sodium-coupled glucose transporter found on the apical surface of kidney, liver, and testis cells. It also acts as a urea channel in the kidney's inner medulla. No confirmed human disease syndrome has been attributed to loss of this gene in the published medical literature.

You carry one copy of a stop-gain variant (p.Leu182Ter) that likely prevents your altered copy from making a full-length transporter protein. Because this follows an autosomal recessive inheritance pattern, your working second copy continues to produce functional MFSD4B protein. No human disease has been linked to having one altered copy of this gene, and no dominant effect has been described. As a heterozygous carrier, your own risk of developing a clinical condition from this variant is low because your other copy compensates. This is most relevant for family planning: if a future partner were also found to carry an altered copy of MFSD4B, each pregnancy would carry a 1-in-4 chance of a child inheriting two non-working copies, which would be worth discussing with a genetic counselor. The only published study touching this gene flagged it as a candidate (not a confirmed finding) in cisplatin-induced hearing and nerve side effects in testicular cancer survivors (PMID: 40913328). This is not something you need to act on now, but it is worth mentioning to an oncologist if you ever need cisplatin-based chemotherapy.

SODIUM-POWERED SUGAR ENTRY INTO CELLS

Why this matters: MFSD4B is the active component in the cellular hexose transport step that uses a sodium gradient to pull glucose into cells. Understanding this pathway shows exactly where your variant has its effect and why other transporters may partially cover the gap.

Think of a cell like a building that needs fuel deliveries. MFSD4B is one doorman who uses the natural rush of sodium flowing inward to drag glucose into the cell at the same time. If this doorman is absent or shortened, other doormen on the same floor may pick up some of the work, though how fully they compensate in your specific tissues is not yet established.



When this pathway is impaired:

If MFSD4B is non-functional, affected cells may receive less glucose via this specific route and urea handling in the kidney may be subtly altered, though no human disease has been confirmed from this disruption.

MST1

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Immune gut signaling	INFORMATIVE	rs142690032	NP_066278.3: p.Arg651Ter	G/A	High Impact

VARIANT POPULATION FREQUENCY: 2/100

MST1 makes macrophage-stimulating protein (MSP), a signal your liver sends into the blood to help immune cells in your gut and bile ducts respond to bacteria. Large genetic studies link MST1 coding variants to inflammatory bowel disease and primary sclerosing cholangitis. Your variant introduces a premature stop in one copy of MST1. Your second copy continues working. The reviewed literature does not describe a defined clinical syndrome from carrying one loss-of-function copy, and your specific variant has not been studied.

GENE EXPRESSION

Most active in: Liver, Kidney, Testis, Pancreas, Spleen

WHAT THIS MEANS FOR YOU

You carry one altered copy of MST1 alongside one fully working copy. MST1 makes a protein called macrophage-stimulating protein, secreted by the liver to help immune cells in your gut respond to bacteria. Your working copy continues to produce this signal, so you are not without it entirely. The MST1 gene is linked to inflammatory bowel disease and a bile duct condition called primary sclerosing cholangitis in large studies, but those links come from a different common variant, not yours. Your specific variant has not been studied, and no clinical syndrome from having one altered copy of MST1 has been described. This finding is informational for now, and no specific monitoring or lifestyle changes are recommended based on current evidence.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Inflammatory Bowel Disease (IBD) / Crohn's Disease / Ulcerative Colitis

Inflammatory bowel disease is a group of chronic conditions in which the immune system attacks the lining of the digestive tract, causing inflammation, abdominal pain, diarrhoea, and periods of flare and remission. Crohn's disease can affect any part of the gut from mouth to anus; ulcerative colitis is confined to the large intestine.

MST1 is an established IBD and ulcerative colitis risk gene. Large population studies, including GWAS and Mendelian randomisation analyses across tens of thousands of people, consistently show that lower circulating MSP protein levels are associated with higher IBD risk (PMID: 36857861; PMID: 39414629). A gene-centric study specifically linked a coding variant in MST1 to both Crohn's disease and ulcerative colitis through impaired immune signalling (PMID: 19079170). That research examined a different, more common variant from yours. Your specific change, p.Arg651Ter, has not been individually studied for IBD risk, and no defined IBD syndrome from carrying one loss-of-function copy of this gene has been described in the literature. Because you carry one working copy, your body still produces MSP. The overall picture is that your variant acts as a risk modifier rather than a high-certainty disease-causing change. If you ever develop persistent gut symptoms, MST1's established role in gut immune regulation makes it worth mentioning to your doctor.

Primary Sclerosing Cholangitis (PSC)

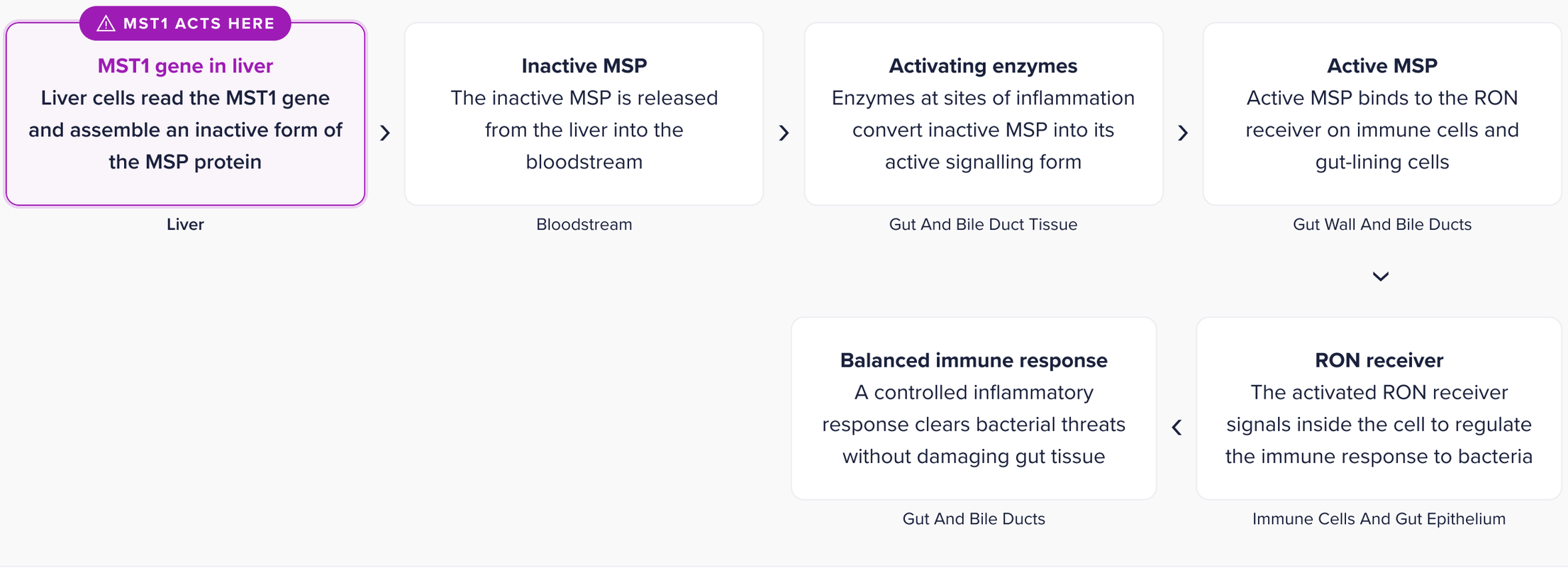
Primary sclerosing cholangitis is a chronic inflammatory condition of the bile ducts inside and outside the liver that causes progressive scarring and narrowing. Over time it can lead to liver damage and is associated with an increased risk of bile duct cancer. It frequently occurs alongside inflammatory bowel disease.

A large GWAS across 1,740 PSC cases and 5,136 controls identified MST1 as one of the strongest non-HLA susceptibility loci for PSC (PMID: 21151127). That study examined a common missense variant in MST1, not your specific variant. Separately, homozygosity for that common variant roughly doubled biliary tract cancer risk, while heterozygous status was not independently associated with that risk in the same cohort (PMID: 23422030). There is no published data on your specific variant and PSC. Your personal risk for PSC cannot be quantified from current evidence. Because MST1 is biologically relevant to bile duct inflammation and your variant is predicted to reduce MSP production from one copy of the gene, it is reasonable to stay aware of PSC symptoms and mention this result to a gastroenterologist if any arise.

THE MSP–RON IMMUNE ALARM PATHWAY

Why this matters: This pathway is the central mechanism by which MST1 variants are thought to contribute to gut and bile duct inflammation. It explains why MST1 consistently appears in genetic studies of IBD and primary sclerosing cholangitis.

Think of MSP as a distress signal your liver sends into the blood when the gut detects bacteria. It travels to immune cells and gut-lining cells, docks onto a receiver called RON, and tells those cells to mount a controlled response. When the signal is weaker, the gut's alarm system may under-respond, allowing inflammation to become poorly regulated.



When this pathway is impaired:

With reduced MSP from one copy of MST1, the gut's immune alarm system may under-respond to bacteria, potentially contributing to poorly regulated inflammation in the gut and bile ducts.

MYCT1

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Cell growth control	INFORMATIVE	rs3841162	NP_079383.2:p.Asp22GlufsTer34	GAGAT/G	High Impact

VARIANT POPULATION FREQUENCY: 15/100

MYCT1 helps your cells know when to stop growing and when to die in an orderly way. It is switched on by c-MYC, one of the body's most powerful growth signals, and then acts as a feedback brake. It is most active in the spleen, lungs, and liver. When silenced inside tumour cells, those cells grow more freely. You have one working and one altered copy. No recognisable clinical syndrome has been linked to inheriting one altered copy, and the gene's population statistics confirm one non-working copy is generally well tolerated.

GENE EXPRESSION

Most active in: Spleen Lung Liver Kidney Colon

WHAT THIS MEANS FOR YOU

You have one working copy and one altered copy of MYCT1, a gene that helps brake runaway cell growth by working downstream of c-MYC, the body's chief growth-control switch. Your altered copy carries a frameshift that results in no usable protein from that copy. Population genetics data show that one non-working copy is common and well-tolerated, and no recognised medical condition has been linked to this in inherited form. Nearly all MYCT1 research involves cancer cell studies and mouse models, not families with inherited copies like yours. There is nothing specific you need to do or avoid right now, but it is worth revisiting as germline research on this gene matures.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Laryngeal neoplasm

Laryngeal neoplasms are tumours of the larynx (voice box), most commonly squamous cell carcinomas arising from the lining of the throat. They can affect voice, swallowing, and breathing, and are strongly associated with tobacco and alcohol exposure.

MYCT1 was originally identified as a candidate tumour suppressor gene in laryngeal squamous cell carcinoma, where it is consistently downregulated in tumour tissue compared with normal tissue (PMID: 22672838). That downregulation is somatic, meaning it happens inside tumour cells during a person's lifetime, not because of a germline variant inherited at birth. Your variant reduces one working copy of MYCT1 in all your cells, but no study has shown that inheriting one altered copy raises the lifetime risk of laryngeal cancer. The gene's population constraint scores (pLI near zero, LOEUF 1.29) indicate that one non-working copy is well tolerated. This is a biologically plausible but currently unproven connection at your zygosity.

Laryngeal squamous cell carcinoma

Laryngeal squamous cell carcinoma is the most common malignant tumour of the larynx, arising from the squamous cells lining the voice box. It accounts for roughly 1–2% of all cancers and is strongly linked to smoking and alcohol use.

MYCT1 was first cloned from laryngeal squamous cell carcinoma tissue and is downregulated in tumours relative to normal tissue (PMID: 22672838). Cell-line studies show MYCT1 suppresses cancer cell migration and invasion through several pathways (PMID: 32659265, PMID: 31152622). All of this evidence is somatic and experimental. No germline study has established that inheriting one altered MYCT1 copy increases your risk of developing this cancer. Tobacco and alcohol remain the dominant modifiable risk factors; avoiding them is the most evidence-based step you can take.

Duodenal ulcer

A duodenal ulcer is a sore that forms in the lining of the first part of the small intestine (the duodenum), usually caused by an imbalance between stomach acid and the protective mucosal lining. Symptoms typically include burning upper abdominal pain, often relieved temporarily by eating.

MYCT1 shows a modest statistical association with duodenal ulcer in Open Targets disease scoring (score 0.31), but this is a computational association and no published study has mechanistically linked germline MYCT1 variants to ulcer risk. Standard risk-reduction measures such as avoiding NSAIDs when possible, not smoking, and testing for Helicobacter pylori if you develop symptoms apply regardless of this variant.

Diabetic nephropathy

Diabetic nephropathy is kidney damage caused by long-standing diabetes, resulting from chronic high blood sugar injuring the small blood vessels of the kidneys. It is a leading cause of chronic kidney disease worldwide.

MYCT1 has a low-level computational association with diabetic nephropathy (Open Targets score 0.08). MYCT1 is expressed in vascular endothelial and smooth muscle cells, and one study found that nitrosative stress, a feature of diabetic vascular disease, downregulates MYCT1 in smooth muscle cells (PMID: 34604957). That study examined cells under stress conditions, not germline variants. No study links inheriting one altered MYCT1 copy to kidney disease risk. Standard diabetes prevention and management remain the relevant actions here.

Abruptio Placentae

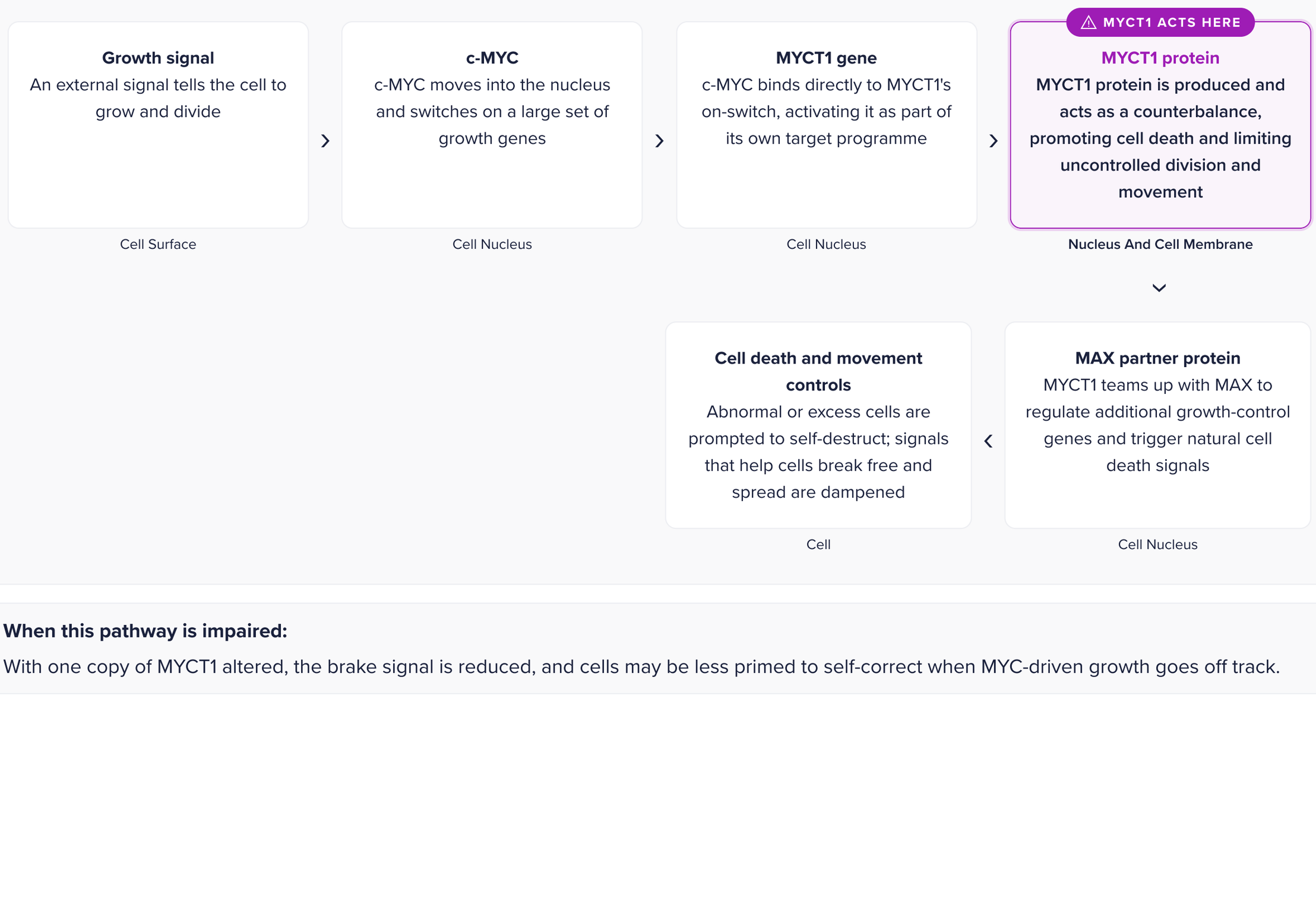
Abruptio placentae (placental abruption) is a pregnancy complication in which the placenta separates from the uterine wall before delivery, which can cause bleeding and restrict oxygen to the baby. It is a significant cause of maternal and foetal complications.

This condition is not applicable to you. The association between MYCT1 and placental abruption appears in a computational disease-scoring database; no mechanistic or clinical study links germline MYCT1 variants to this condition.

THE MYC GROWTH-BRAKE FEEDBACK LOOP

Why this matters: This pathway is the core mechanism through which MYCT1 functions. It shows how your body uses MYCT1 to put the brakes on the same growth signal that switches MYCT1 on in the first place.

Think of c-MYC as a gas pedal in your cells, telling them to grow and divide. MYCT1 is part of the braking system that c-MYC itself switches on, keeping growth under control and helping trigger orderly removal of damaged cells. When MYCT1 is silenced or missing, that brake is weaker.



When this pathway is impaired:

With one copy of MYCT1 altered, the brake signal is reduced, and cells may be less primed to self-correct when MYC-driven growth goes off track.

NOXO1

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Immune ROS signaling	INFORMATIVE	rs200352693	NP_751907.1:p.His193ProfsTer38	GT/G	High Impact

VARIANT POPULATION FREQUENCY: 2/100

NOXO1 is the "organizer" subunit of a superoxide-generating enzyme complex built around NOX1 and NOX3. It is found mainly in your colon lining, blood vessel walls, inner ear, and testes. Think of it as a docking scaffold: without it, the complex cannot assemble and its controlled chemical signal drops. You carry one altered copy of NOXO1 alongside one working copy. This variant is currently classified as Uncertain Significance, meaning science has not yet established whether reduced activity from one copy causes any defined human disease.

GENE EXPRESSION

Most active in: Colon, Testis, Liver, Kidney, Lung

WHAT THIS MEANS FOR YOU

You carry one altered copy of NOXO1, a gene that helps assemble the machinery your cells use to produce small, controlled bursts of reactive oxygen molecules. These act as chemical signals in immune responses and cell growth. Your second copy of NOXO1 is intact and continues producing functional protein, largely compensating for the altered copy. The literature does not document any symptoms or measurable health difference in people with one non-working copy, and population data confirms this is well tolerated. Mouse studies removing both copies showed effects on blood pressure and inflammation, but those findings do not translate directly to your situation. This variant is Uncertain Significance, meaning it is not yet well enough studied in humans to indicate any health problem.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

congenital cataract-progressive muscular hypotonia-hearing loss-developmental delay syndrome

A rare, multi-system syndrome present from birth, characterised by clouding of the eye's lens (cataract), low muscle tone that tends to worsen over time, sensorineural hearing loss, and delayed cognitive and motor development. It typically requires lifelong specialist care across multiple disciplines.

NOXO1 appears in a large variant database association list for this syndrome, but no published human research directly links NOXO1 loss-of-function variants to this condition, and no formal gene-disease validity assessment has been established. You carry one non-working copy of NOXO1 while your second copy remains intact and continues to produce functional protein. The gene's constraint score (LOEUF approximately 1.5) indicates that one non-working copy is well tolerated across the general population. At present, your variant does not establish a diagnosis of, or a meaningfully elevated risk for, this syndrome. This association is speculative and should not be a source of concern.

mitochondrial disease

A broad category of disorders caused by impaired energy production in the mitochondria, the cell's power generators. Symptoms can affect almost any organ but most often involve muscles, the brain, the heart, and the eyes, because these tissues have the highest energy demands.

NOXO1 carries a weak statistical association with mitochondrial disease in large variant databases, but no published research establishes a mechanistic or clinical link between heterozygous NOXO1 loss-of-function and mitochondrial dysfunction in humans. Your intact second copy continues to operate normally. This association does not constitute a diagnosis and requires no specific action on your part at this time.

atherosclerosis

A condition in which fatty deposits gradually build up inside artery walls, narrowing and stiffening them over time. It underlies most heart attacks and strokes and develops slowly over decades, driven by a combination of lifestyle factors, blood pressure, cholesterol levels, and genetics.

Mouse studies found that complete deletion of both NoxO1 copies reduced plaque formation and pro-inflammatory markers, but this effect appeared only in female mice and not in males (PMID: 32949971). Since you are male and carry only one non-working copy rather than a complete deletion, this animal finding cannot be meaningfully applied to your situation. No human study has examined atherosclerosis risk in people who carry one non-working NOXO1 copy. Standard cardiovascular risk management, including knowing your cholesterol and blood pressure numbers, eating well, staying physically active, and not smoking, remains the most evidence-based approach for you.

diabetes mellitus

A group of metabolic conditions defined by persistently elevated blood sugar. Type 2 diabetes, the most common form, develops when cells become resistant to insulin and the pancreas cannot compensate, leading over time to damage in blood vessels and nerves throughout the body.

Mouse experiments found that complete NoxO1 knockout protected against diabetes-induced vascular dysfunction and helped maintain lower blood pressure (PMID: 29195137). These findings come from animals with no working copies of the gene, and no equivalent human data exist for people who carry one non-working copy as you do. This association is background context only and does not represent an established risk tied to your variant.

THE NOX1 SUPEROXIDE ASSEMBLY LINE

Why this matters: This is the central pathway through which NOXO1 acts. Understanding it explains what the gene does and what happens when your copy of the organizer piece is reduced.

Imagine a small factory inside the cell wall that converts a cellular fuel into a controlled burst of reactive oxygen molecules. Those molecules act as chemical signals, helping regulate how quickly cells divide and how the immune system behaves. NOXO1 is the factory foreman who calls all the worker proteins to their stations. Without a foreman, the workers scatter and the factory output drops.

NADPH (cellular fuel)
Sits inside the cell, ready to donate electrons to start the reaction

Cell Interior

›

NOX1 + p22phox (the engine)
Two membrane proteins pair up to form the core engine embedded in the cell wall

Cell Membrane

›

⚠ NOXO1 ACTS HERE

NOXO1 (the organizer)
Latches onto membrane fats via its PX domain and holds the activator protein in place, assembling the full complex

Cell Membrane

›

NOXA1 (the activator)
Slots into place once NOXO1 is anchored, switching the engine to 'on'

Cell Membrane

⌄

RAC GTPase (the ignition key)
Provides the final activation signal to run the engine at full speed when the cell calls for it

Cell Membrane

‹

Superoxide (the output signal)
Electrons pass from NADPH through the engine to oxygen outside the cell, creating superoxide, a chemical messenger for cell growth and immune signalling

Outside Cell Membrane

When this pathway is impaired:

With reduced NOXO1, the complex assembles less efficiently, producing less superoxide signal in affected tissues.

OR2D3

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Smell detection	INFORMATIVE	rs59264610	NP_001004684.1:p.Leu121PhefsTer13	TC/T	High Impact

VARIANT POPULATION FREQUENCY: 12/100

OR2D3 is one of roughly 400 functional smell-detecting genes in your genome. It encodes a receptor that sits on the surface of specialised cells lining your nose, waiting for a specific odour molecule to arrive. When that molecule docks, the receptor fires a signal toward your brain, contributing one small piece to your overall sense of smell. Think of it as one instrument in a very large orchestra: if a single violin plays a little more quietly, the symphony continues. No medical condition has been linked to having one altered copy of this gene.

GENE EXPRESSION

Most active in: Kidney, Liver, Lung, Colon, Pancreas

WHAT THIS MEANS FOR YOU

You carry one altered copy of OR2D3, a gene encoding a single odorant receptor, one of roughly 400 your nose uses to detect smells. Your second copy is intact and keeps producing functional protein. Because so many receptors work in parallel, losing activity from one typically has only a subtle effect on smell. No clinical condition has been documented for someone with one non-working copy of this gene. The statistical link to male reproductive organ cancer in a gene-annotation database is not backed by any published OR2D3 clinical study and is not a reason for concern. This finding does not require any changes to your daily life or medical care.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Olfactory receptor dysfunction (OR2D3-related)

Olfactory receptor dysfunction refers to a reduced ability to detect or distinguish specific odour molecules. The olfactory system relies on roughly 400 expressed receptor proteins, each tuned to a different set of chemical cues. When one receptor gene is non-functional, the remaining receptors partially compensate, so the impact on overall smell is usually subtle rather than complete.

You are a heterozygous carrier of a loss-of-function variant in OR2D3, meaning you have one working copy and one non-functional copy. Because this gene follows an autosomal recessive inheritance pattern, your working copy continues to produce functional OR2D3 receptor protein in your olfactory sensory neurons. No clinical condition has been documented in the reviewed literature for people who carry a single altered copy of this gene. At most, you might have a mildly reduced sensitivity to a very narrow set of odour molecules that OR2D3 specifically recognises, but even that has not been formally established for this gene in published research. This is not a disease diagnosis. From a family planning perspective, if a future biological child inherited a loss-of-function variant in OR2D3 from both parents, the expected consequence would most likely relate to smell sensitivity rather than any broader health concern, though even that biallelic state has not been formally characterised. If this is relevant to your family planning decisions, a genetics counsellor can discuss partner carrier testing. (PMID: 29534194)

Male reproductive organ cancer (OpenTargets association, score 0.27)

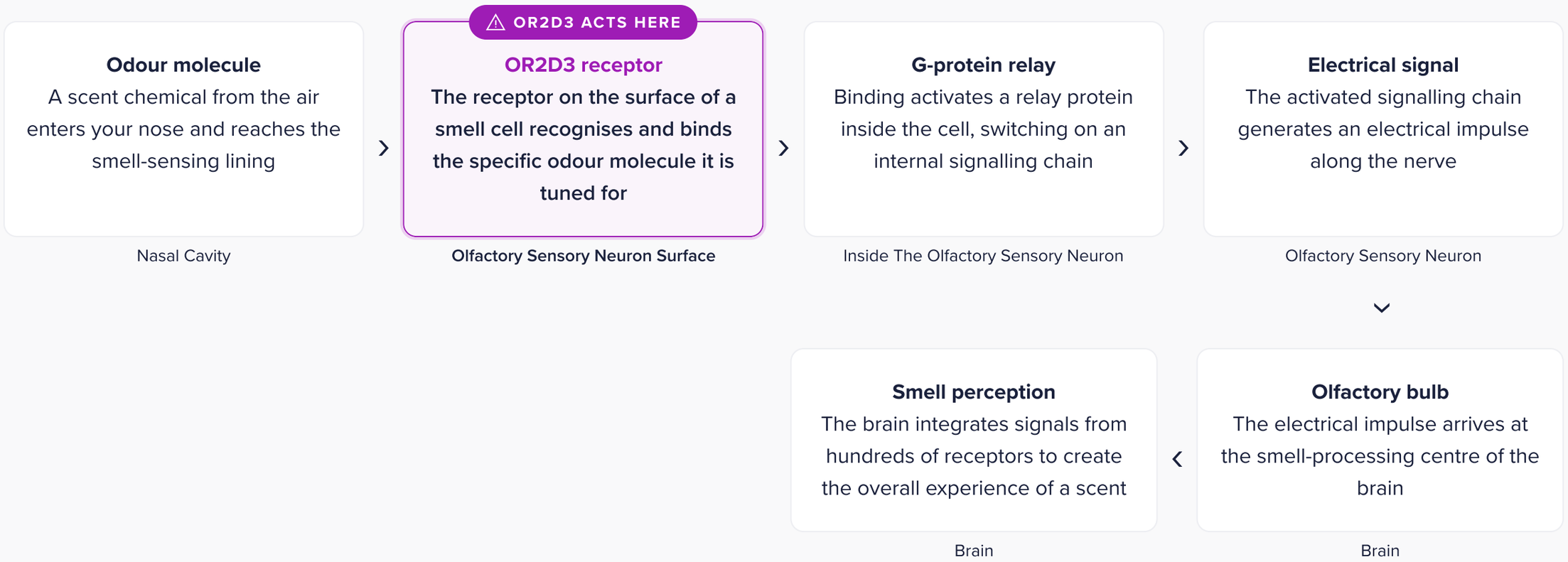
Male reproductive organ cancers are a broad category that includes testicular cancer and prostate cancer, among others. They arise from abnormal cell growth in reproductive tissues and vary widely in prognosis and treatment depending on type and stage.

OpenTargets lists a statistical association between OR2D3 and male reproductive organ cancer with a confidence score of 0.27 out of 1.0. This is a weak, exploratory signal derived from large population-level genomic datasets, not a clinically validated finding. No published study has established OR2D3 as a causative or high-risk gene for any reproductive cancer, and no biological mechanism has been described linking this variant to increased cancer risk. This association is not currently actionable. Standard age-appropriate cancer screening recommended by your doctor for a healthy 37-year-old man remains the appropriate approach, and this variant does not change those recommendations based on current evidence.

SMELL DETECTION

Why this matters: This is the only well-characterised pathway OR2D3 participates in. Understanding how smell signals travel from your nose to your brain explains what, if anything, this variant might change for you.

Think of your nose as having hundreds of different locks, each designed to recognise a specific key (odour molecule). OR2D3 is one of those locks. When the right key fits, the lock opens a door that sends a message to your brain. With one less working OR2D3 lock available, some very specific odour keys may be slightly harder to detect, but the hundreds of other locks in your nose continue doing their jobs.



When this pathway is impaired:

One copy of the OR2D3 receptor is non-functional, potentially reducing detection of the narrow set of odour molecules it normally recognises. The impact on overall smell is expected to be minimal because many other receptors compensate.

OR2T35

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Smell detection	INFORMATIVE	1-248576305-248647941-C-<DEL>-CNV	NP_001001827.1	N/<DEL>	High Impact

OR2T35 makes an odorant receptor protein, a molecular sensor that sits on the surface of cells and detects specific scent molecules. While best known for its role in the nose, this receptor is also expressed in the kidney, liver, and lung. You have one working copy of this gene and one copy that has been deleted. No established clinical condition is linked to losing one copy of OR2T35 in current medical literature, and the missense constraint flag is a biological observation that does not translate into a clinical recommendation on its own.

GENE EXPRESSION

Most active in: Liver · Lung · Colon · Pancreas · Kidney

WHAT THIS MEANS FOR YOU

You have a deletion removing one of your two copies of OR2T35, a gene that makes a smell-detecting receptor protein in the nose. Your remaining copy still produces functional receptor, and the olfactory system has hundreds of receptor types working in parallel, so single-copy loss of one receptor is very unlikely to affect your sense of smell or your general health. No clinical disease has been linked to carrying one non-working copy in reviewed literature. The only meaningful implication is for family planning: if a future co-parent also carries a loss-of-function change in OR2T35, a child could inherit two non-working copies. What that would mean clinically is still unknown. This finding is informational rather than a health concern today.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Olfactory receptor loss-of-function (OR2T35, heterozygous deletion)

Olfactory receptor genes encode sensor proteins in the nose that detect specific odour molecules and transmit smell signals to the brain. There are hundreds of these receptor genes in the human genome, and they form a large, highly redundant family. Loss of any single receptor gene is generally not expected to abolish smell on its own.

You carry one deleted copy and one working copy of OR2T35. Because the olfactory receptor gene family is so large and overlapping, your one intact copy continues to make functional receptor protein. No clinical disease syndrome has been linked to single-copy loss of OR2T35 in any published study. The one time this variant appeared in the literature, it was noted as a background finding with no symptoms attributed to it (PMID: 37109656). Your personal health risk from this variant appears to be very low. The most relevant implication for you right now is family planning: if a future biological co-parent also carries a non-working copy of OR2T35, there would be a 1-in-4 chance a child could inherit two deleted copies. What two deleted copies would mean clinically is genuinely unknown at this point. A brief conversation with a clinical geneticist before starting a family is a sensible step.

Neurodegenerative disease association (OR2T35, statistical signal only)

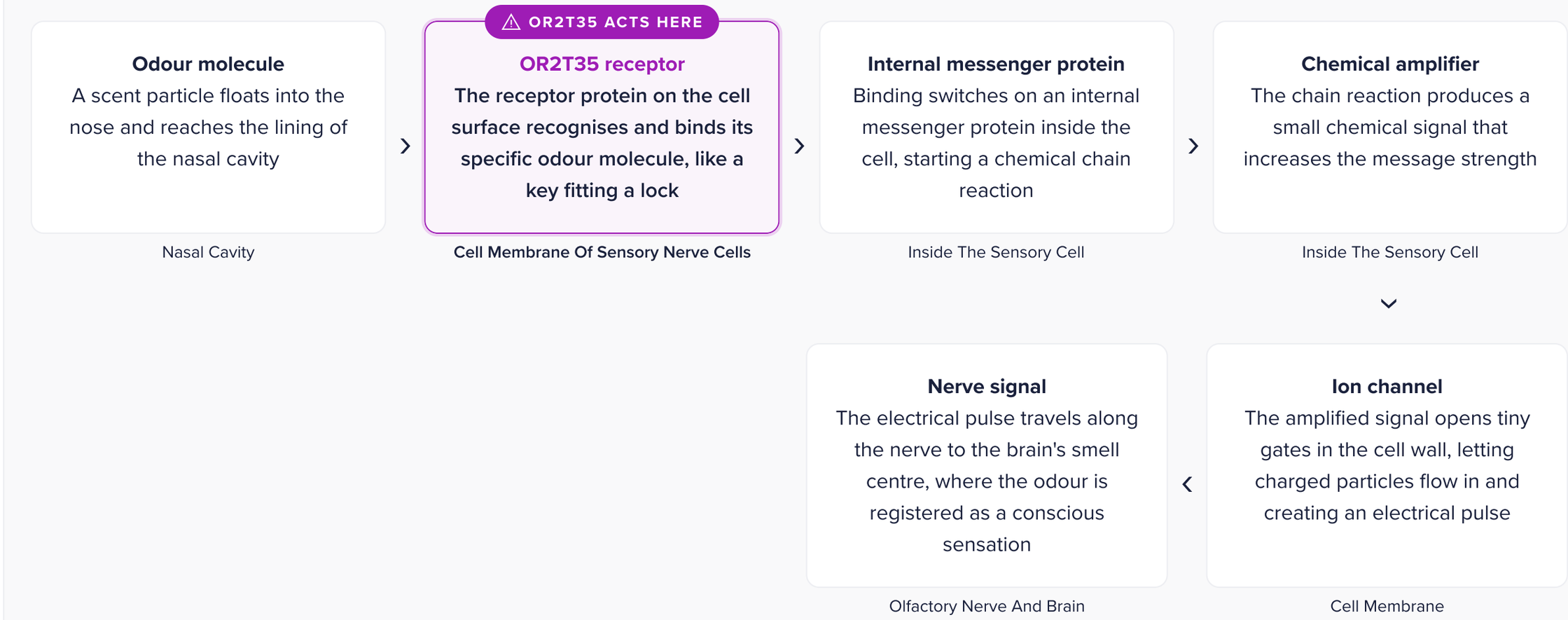
Neurodegenerative diseases are a broad group of conditions in which nerve cells progressively lose function over time, affecting movement, cognition, or both. Examples include Parkinson's disease and Alzheimer's disease. There is emerging scientific interest in whether olfactory receptor genes play any role in these conditions, given that smell loss can be an early feature of some neurodegenerative diseases.

A large-scale data-mining platform flags a weak statistical association between OR2T35 and neurodegenerative disease, with a score of 0.37 out of 1. This is a low score and reflects a statistical pattern in population data, not a proven biological mechanism. There are no published studies showing that carrying one deleted copy of OR2T35 increases your risk of any neurodegenerative condition. This signal is not strong enough to change your screening or monitoring routine, and no specialist guideline recommends action based on it. It is worth mentioning to your doctor so it can be noted in your record, but it does not call for any urgent concern or change in your health routine.

SMELL DETECTION AND SIGNAL SENDING

Why this matters: OR2T35 sits at the very first step of how your body turns a smell molecule into a conscious sensation. Understanding this pathway shows what the receptor normally does and where things may be altered when one copy is missing.

Think of your nose as a security gate with thousands of different scanners, each built to recognise a specific type of visitor (an odour molecule). OR2T35 is one of those scanners. When its matching odour molecule arrives, it presses a button that sends an electrical message up to the brain saying 'smell detected'. With one scanner removed, the gate still works — it just has one fewer detector for the molecules OR2T35 would normally recognise.



When this pathway is impaired:

With one copy of OR2T35 deleted, fewer of these receptors are available. The specific odour molecules OR2T35 normally detects may trigger a weaker signal, though the rest of the pathway continues to function normally.

KEY ACTIONS

There are no specific medical actions required based on this variant. If you are planning to have biological children and want to explore the small theoretical family-planning consideration in more detail, a single conversation with a clinical geneticist is a reasonable step. No monitoring, dietary changes, or specialist follow-up are indicated by current evidence.

OR5B3

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Smell detection	INFORMATIVE	rs200799158	NP_001005469.1:p.Phe31SerfsTer16	AG/A	High Impact

VARIANT POPULATION FREQUENCY: 4/100

OR5B3 makes a receptor protein best known for detecting odour molecules in your nose as part of your sense of smell. It is one of hundreds of odorant receptors your body uses, each tuned to certain smells. The gene is also expressed in your kidney, liver, and lung, hinting at broader roles, but what those are in living humans is not yet well understood. No recognised Mendelian disease has been linked to this gene.

GENE EXPRESSION

Most active in: Kidney · Liver · Lung · Colon · Pancreas

WHAT THIS MEANS FOR YOU

You carry one altered copy of OR5B3 alongside one fully working copy. This gene provides a receptor in your nose that helps detect specific odour molecules, like one lock among hundreds, each matched to a different scent key. Because the gene follows an autosomal recessive pattern, one working copy is generally sufficient, and no clinical health condition from having a single altered copy has been documented. One small exploratory study linked OR5B3 to pressure-pain sensitivity, but that signal is preliminary and cannot be translated into a personal health warning. This result is most relevant to family planning, as a child would need two non-working copies to be affected. No monitoring or treatment is indicated.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Odorant receptor dysfunction / olfactory signal reduction

The olfactory system relies on hundreds of different receptor proteins, each tuned to detect specific odour molecules. When one of these receptors is altered or absent, the nose may have reduced sensitivity to the particular smells that receptor normally detects. Because humans have a large and overlapping family of smell receptors, losing one receptor does not necessarily cause noticeable smell loss.

You have one working copy and one frameshift copy of OR5B3. OR5B3 follows an autosomal recessive inheritance pattern, meaning one working copy is generally sufficient. No clinical syndrome from having a single altered copy of this gene has been published in the reviewed literature. The most likely real-world consequence, if any, would be subtly reduced sensitivity to a narrow set of specific odours, and this may not be noticeable in everyday life given the redundancy of your roughly 400 other smell receptors. As a heterozygous carrier, your own risk of developing a clinical condition is low. This result is most relevant for family planning: if your partner also carries a loss-of-function variant in OR5B3, your children would have a 25% chance of inheriting two non-working copies.

Pain sensitisation (exploratory GWAS association)

Pain sensitisation refers to a state in which the nervous system becomes more responsive to pain signals, lowering the threshold at which pressure or other stimuli are perceived as painful. It is studied in the context of conditions such as osteoarthritis and persistent post-surgical pain. The genetic contributors to this trait are still being mapped, and no single gene has been confirmed as a major causal driver.

A genome-wide gene-based association study in 933 participants found OR5B3 as the top statistical signal for pressure-pain detection thresholds measured at the anterior tibia, a marker of widespread pain sensitisation (PMID: 34958702). This is a single exploratory study with a small sample, no replication, and no mechanistic explanation for why an odorant receptor gene would influence pain thresholds. This association cannot be translated into a personal health prediction for you. It is worth being aware of as emerging science, but it does not currently warrant any clinical action.

ODOUR DETECTION AND SMELL SIGNALLING

Why this matters: OR5B3 is a receptor in the pathway that converts an odour molecule into a nerve signal your brain reads as a smell. Understanding this pathway explains what the receptor normally does and where your variant has its effect.

Think of your nose's smell-sensing cells like a row of locks on a door, each designed to recognise a specific key (an odour molecule). OR5B3 is one of those locks. When the right odour key fits, the lock opens a chain of chemical events inside the cell, sending a signal to your brain that says 'that smell is here'. With one altered copy of this gene, you have fewer of these particular locks available.

When this pathway is impaired:

With one altered copy of OR5B3, fewer working receptors are available for the specific odour(s) this receptor normally detects. Whether one working copy is sufficient to maintain normal smell perception is not established in the reviewed literature.

PCSK4

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Reproductive function	INFORMATIVE	rs200944148	NP_060043.2: p.Gln141Ter	G/A	High Impact

VARIANT POPULATION FREQUENCY: 8/100,000

PCSK4 is a molecular scissors enzyme that snips inactive proteins into their active forms. It is most active in sperm, sitting on the acrosome, the capsule at the sperm tip loaded with tools needed to reach an egg. When both copies are knocked out in mice, males are infertile because those tools are never properly activated. You carry one altered copy and one working copy. Your working copy continues to produce functional PCSK4, and the gene's constraint data confirm it is not dose-sensitive in the way disease-causing dominant genes are.

GENE EXPRESSION

Most active in: Testis Liver Kidney Pancreas Colon

WHAT THIS MEANS FOR YOU

You carry one working copy of PCSK4 and one copy with a premature stop codon. Because this gene follows an autosomal recessive pattern, a single altered copy is generally well tolerated. Your working copy still produces the functional enzyme, which activates proteins in the tip of sperm cells that are needed to reach and penetrate an egg. The science here comes mainly from mice where both copies were removed, causing infertility. No clinical syndrome has been found in people with just one altered copy, and the gene's constraint score confirms this is expected to be well tolerated. This finding is largely informational. The main relevance is family planning: if your biological partner also carries a PCSK4 loss-of-function variant, future children could inherit two non-working copies.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Spermatogenic failure 72

Spermatogenic failure describes an inability or reduced ability of sperm to complete the steps required to fertilize an egg. This can include defects in the acrosome reaction, sperm capacitation, and the sperm's ability to bind and penetrate the egg's outer shell. These failures can result in difficulty conceiving naturally.

As a heterozygous carrier of a loss-of-function variant in PCSK4, your own risk of developing this condition is low because your other copy continues to produce functional enzyme. The strong infertility phenotype documented in research comes from mouse models where both copies are completely knocked out (PMID: 19109312), and no clinical syndrome has been documented in people who carry a single altered copy. The gene's constraint score (LOEUF ~0.98) confirms that heterozygous loss is generally well tolerated. If you ever experience unexplained difficulty conceiving, this variant is worth mentioning to a reproductive specialist as useful context, but it does not by itself establish a diagnosis or confirm a fertility problem. The most practical implication is for family planning: if your biological partner also carries a loss-of-function variant in PCSK4, each pregnancy would carry a 1-in-4 chance of a child inheriting two non-working copies. Discussing partner carrier screening with a genetics or reproductive specialist is a reasonable next step if you are planning to have biological children.

Azoospermia

Azoospermia is the complete absence of sperm in ejaculated semen. It is one of the most severe forms of male infertility and can result from problems with sperm production in the testes or from blockages that prevent sperm from being released.

PCSK4 has a modest statistical association with azoospermia in large population datasets (OpenTargets score 0.10). The biological connection is plausible given PCSK4's role in sperm function, but complete azoospermia in the published literature is linked to biallelic loss of sperm-related genes, not to carrying a single altered copy. No human clinical series has documented azoospermia specifically in people with one non-working copy of PCSK4. This association is noted for completeness, but it is not an established diagnosis based on this variant alone. If you have any concerns about sperm count or fertility, a semen analysis is the straightforward first step and is worth discussing with your doctor.

Breast ductal adenocarcinoma

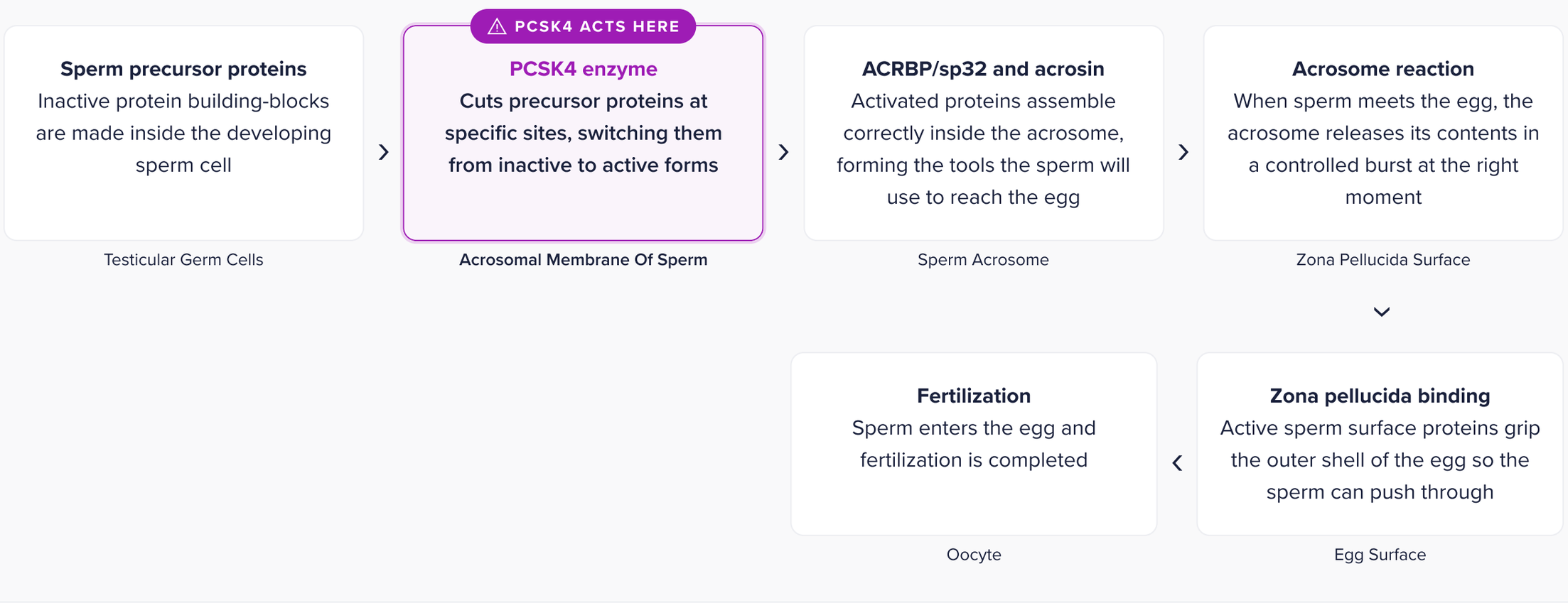
Breast ductal adenocarcinoma is the most common type of breast cancer, originating in the cells lining the milk ducts. It can be non-invasive (in situ) or invasive, where cancer cells spread beyond the duct into surrounding tissue.

PCSK4 has a weak statistical association with breast ductal adenocarcinoma in large genomic databases (OpenTargets score 0.11), but this is a population-level correlation rather than an established causal link. No mechanism has been confirmed that ties PCSK4 loss-of-function specifically to breast cancer risk, and no clinical guidelines recommend breast cancer screening based on PCSK4 variants. As a 37-year-old male, your background risk for breast cancer is already very low. This association is not currently actionable, and no changes to your screening routine are indicated on the basis of this variant alone. If you have a personal or family history of breast cancer, discuss that separately with your doctor, as other well-established genes would be far more relevant.

SPERM ACTIVATION AND EGG PENETRATION

Why this matters: This is the pathway where PCSK4 does its most important work. Complete loss in mouse models causes fertilization failure at precisely the step where PCSK4 activates acrosomal proteins, making it central to understanding what this gene does.

Think of sperm reaching an egg like a delivery driver who needs the right tools to open a locked door. Before the sperm arrives at the egg, special proteins inside its tip have to be switched from an inactive to an active form. PCSK4 is the enzyme that flips that switch. When PCSK4 is completely absent in mice, the tools never get activated properly, and the sperm cannot open the door.



When this pathway is impaired:

When PCSK4 is completely absent, acrosomal proteins are not properly activated, the acrosome reaction fires too early, and sperm cannot grip or penetrate the egg's outer shell.

KEY ACTIONS

Because no symptoms or clinical risks are established for carrying a single altered copy of PCSK4, there are no urgent medical steps to take right now. If you and your partner are planning children, asking your doctor about carrier screening for your partner is a reasonable step. If you ever experience unexplained difficulty conceiving, mentioning this variant to a reproductive specialist provides useful context, though this finding alone does not establish a cause.

POTEA

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Cancer/testis signaling	INFORMATIVE	rs557897303	XP_024302914.1:p.Asp430IlefsTer43	AG/A	High Impact

VARIANT POPULATION FREQUENCY: 4/10,000

POTEA belongs to the POTE gene family, unique to primates, and is normally active in the testis, prostate, ovary, and placenta. In most tissues it stays switched off, then reactivates in certain cancers, making it a target of immunotherapy research. One population study raised a signal linking POTEA variants to colorectal cancer risk, but there is no confirmed clinical syndrome, no ClinVar entry, and no documented symptoms in people with one altered copy. The evidence is early-stage.

GENE EXPRESSION

Most active in: Testis Kidney Liver Lung Colon

WHAT THIS MEANS FOR YOU

You carry one altered copy of POTEA alongside one working copy. POTEA is normally active in the testis and a few reproductive tissues, helping maintain cell structure. The only published human data comes from one Swedish population study flagging a POTEA variant as a possible colorectal cancer contributor, but that signal is preliminary and no confirmed syndrome exists for carrying one altered copy. Your working copy continues to function. This finding is currently informational; it does not change your daily medical care on its own. Keeping up with standard colorectal cancer screening, as recommended for all men your age, is the most grounded step you can take.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Colorectal Cancer (candidate susceptibility signal)

Colorectal cancer is a malignancy arising from the lining of the large intestine or rectum. It is one of the most common cancers worldwide and develops through a combination of genetic, lifestyle, and environmental factors. Most cases are sporadic, but a meaningful fraction involves inherited susceptibility.

- **Your variant sits in a gene flagged as a candidate colorectal cancer risk signal in a single Swedish population study of roughly 1,500 CRC patients and 12,000 controls. That study reported odds ratios of 2.0 to 17.6 across seven candidate genes, but an individual figure for POTEA alone has not been published, and the inheritance pattern described was complex rather than straightforwardly dominant. This is hypothesis-generating evidence only. No clinical body has recognised POTEA as an established colorectal cancer risk gene, and no management guidelines exist for this variant. In practical terms, your colorectal cancer screening should follow standard age-appropriate recommendations, with the option to discuss your family history with a gastroenterologist if close relatives have had CRC. (PMID: 29547645)**

Cancer/Testis Antigen Re-expression (tumour biology context)

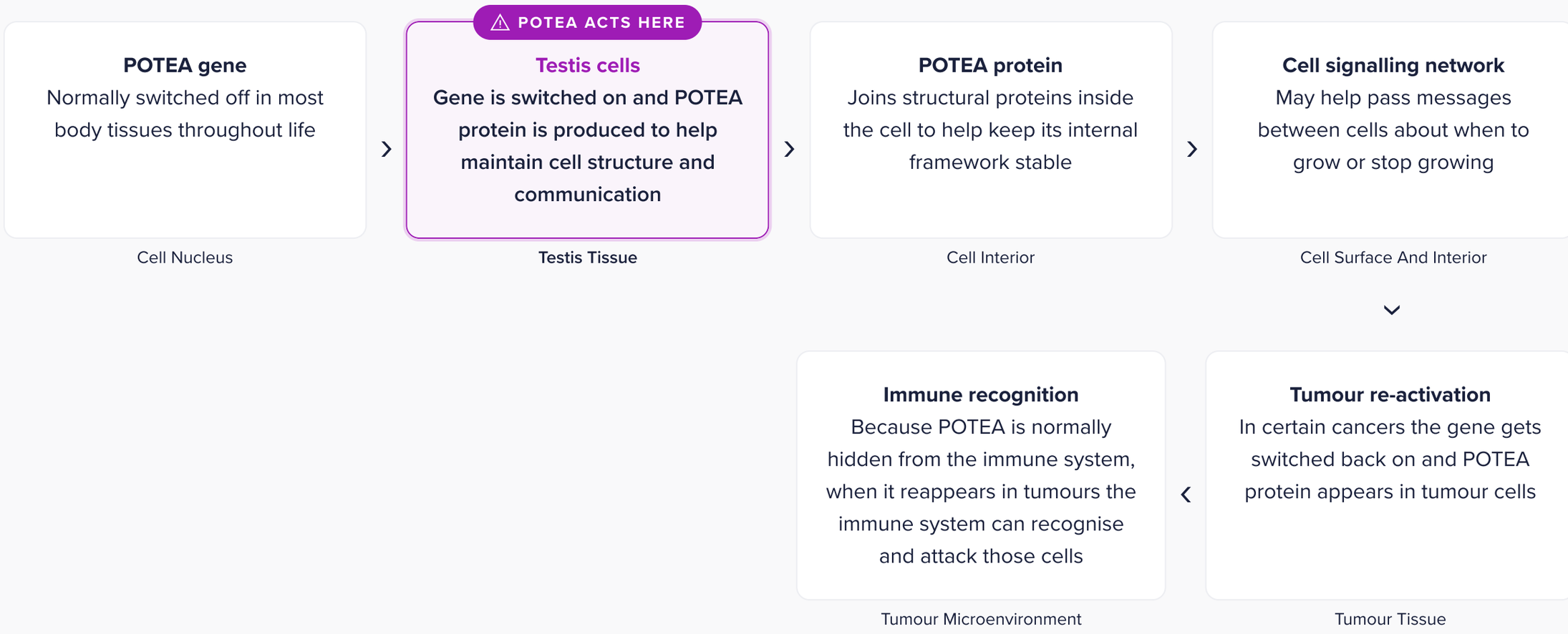
Cancer/testis antigens are proteins normally expressed only in the testis and placenta that become re-expressed in a wide range of tumour types, including lung, bladder, and skin cancers. Because they are absent from most healthy adult tissues, they are studied intensively as targets for cancer immunotherapy, including mRNA vaccines and cellular therapy approaches.

- **POTEA belongs to the POTE family of cancer/testis antigens. Normally the gene is active in testis tissue, which is relevant to you as a male. In various cancers, POTE-family proteins get switched back on in tissues where they do not normally belong, and they have been explored as immunotherapy targets and prognostic markers. One study in renal cell carcinoma found that an immune response against POTEA correlated with better survival outcomes. (PMID: 37545223) What this means for you personally is not yet clear: the re-expression biology is studied at the population and tumour level, not at the level of individuals carrying one altered copy. Your other copy of POTEA continues to work, and no clinical consequence of heterozygous loss has been described in published literature. This is scientific context, not an actionable finding on its own. (PMID: 33910064)**

CANCER/TESTIS ANTIGEN SWITCH

Why this matters: POTEA is classified as a cancer/testis antigen, meaning it is normally locked away and only expressed in the testis, then reactivated in certain tumours. This on/off switching pattern is the most clinically relevant framework for interpreting your variant.

Think of POTEA as a specialist tool kept locked in a drawer that only opens in the testis. In some cancers, that lock gets broken and the tool appears elsewhere. Your variant means one copy of the tool may be broken or missing, which could matter in any tissue where the gene gets switched back on.



When this pathway is impaired:

With one altered copy, reduced POTEA protein may be available in testis tissue and in any tumour context where re-activation occurs. The exact clinical consequence is not yet established.

SMIM22

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Lipid droplet regulation	INFORMATIVE	rs778473760	NP_001240723.1:p.Gly42AlafsTer30	AG|A	High Impact

VARIANT POPULATION FREQUENCY: 2/1,000

SMIM22 makes a small protein in the late endosome membrane. Its known role is helping regulate fat-droplet formation inside cells, likely by interacting with SQLE, an enzyme in the cholesterol pathway. In several cancers, SMIM22 is reduced in tumour tissue and lower expression correlates with more aggressive disease in observational studies. No inherited clinical condition caused by germline SMIM22 variants has been described, so the significance of your specific variant is currently uncertain.

GENE EXPRESSION

Most active in: Colon, Pancreas, Kidney, Testis, Lung

WHAT THIS MEANS FOR YOU

You have a frameshift variant in SMIM22, a gene that makes a small protein helping cells fine-tune lipid droplet formation, their internal fuel-storage structures, through an interaction with a cholesterol-synthesis enzyme. Your variant likely prevents this copy from making a working protein. However, no inherited health condition has ever been linked to germline variants in SMIM22. All published studies examined SMIM22 expression changes inside tumour tissue, not in people born with variants like yours. The laboratory also flagged your zygosity as uncertain. This finding is best understood as a variant of uncertain significance in a gene whose role in inherited disease is not yet established, and it does not call for any changes to your daily life right now.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Neurodegenerative disease

Neurodegenerative diseases are a broad group of conditions in which nerve cells in the brain or spinal cord progressively lose function and die, leading to problems with movement, memory, or cognition. Examples include Alzheimer's disease and Parkinson's disease.

SMIM22 has a weak statistical association with neurodegenerative disease in a gene-scoring database (OpenTargets score 0.32), but this signal comes from bioinformatics modelling, not from studies of people with inherited SMIM22 variants. No mechanism linking your specific frameshift variant to neurodegeneration has been described, and no inherited neurological syndrome has been attributed to germline SMIM22 loss of function. This association is noted for completeness, but it does not currently change your medical care. Mention it to your doctor so it can be revisited as research matures.

Non-small cell lung carcinoma

Non-small cell lung carcinoma is the most common type of lung cancer, accounting for roughly 85% of all lung cancer cases. It encompasses several subtypes including adenocarcinoma and squamous cell carcinoma, and can affect breathing, cause a persistent cough, or spread to other organs.

Published studies show that SMIM22 expression within tumour tissue is altered in non-small cell lung cancer, and one study linked SMIM22 methylation status to survival outcomes in lung squamous cell carcinoma using population-level genomic data (PMID: 39711312). These are somatic findings inside tumour cells, not studies of people born with a germline variant like yours. Whether your inherited frameshift meaningfully changes your personal lung cancer risk is not yet known. Standard age-appropriate cancer screening and avoiding smoking remain the most evidence-based steps you can take.

Autosomal recessive nonsyndromic hearing loss 9

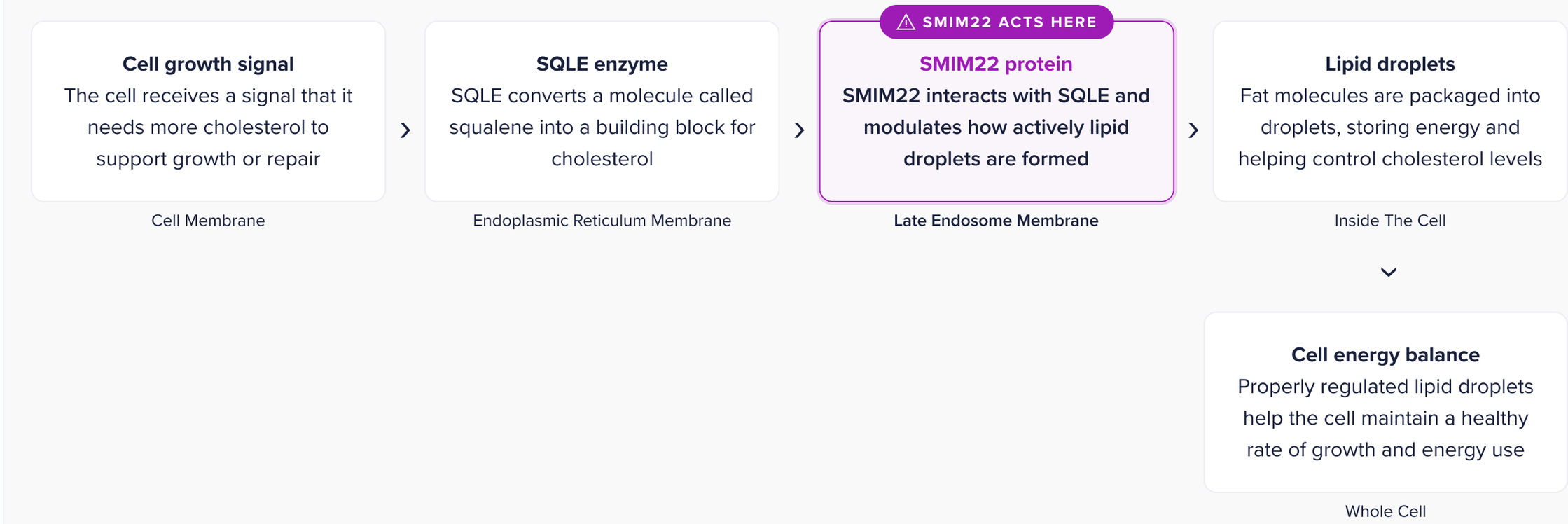
Autosomal recessive nonsyndromic hearing loss 9 is a form of inherited hearing loss that affects the inner ear without involving other organ systems. It is caused by inheriting two non-working copies of a gene and typically presents in childhood, ranging from mild to profound hearing impairment.

This condition appears as a low-scoring OpenTargets association for SMIM22 (score 0.05), but it is not a recognised or curated gene-disease relationship. There is no ClinGen validity assessment, no GeneReviews chapter, and no published evidence linking germline SMIM22 variants to hearing loss in people. This entry likely reflects background bioinformatics noise rather than a true clinical connection. No hearing-specific monitoring beyond routine care is recommended on the basis of this finding alone.

LIPID DROPLET REGULATION VIA SQLE INTERACTION

Why this matters: The only documented molecular role for SMIM22 is modulating lipid droplet formation through its interaction with SQLE. Understanding this pathway is the most direct route to appreciating what the gene does and what its loss might mean at the cellular level.

Think of lipid droplets as tiny fuel storage tanks inside your cells. SQLE is a worker that helps build cholesterol, which cells need in carefully controlled amounts. SMIM22 sits near that worker and appears to act like a volume dial for fat-droplet activity. When SMIM22 is absent or altered, that dial may become unresponsive.



When this pathway is impaired:

Without normal SMIM22, the fine-tuning of lipid droplet formation through SQLE may be lost, potentially disturbing the cell's energy and growth balance.

SMIM22

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Lipid droplet regulation	INFORMATIVE	rs745437189	NP_001240723.1:p.Thr43SerfsTer27	ACCGTGCT|A	High Impact

VARIANT POPULATION FREQUENCY: 2/1,000

SMIM22 makes a small protein embedded in cell membranes, found mainly in compartments called late endosomes. Its documented role is helping regulate how cells form lipid droplets, likely through interaction with SQLE, an enzyme in the cholesterol pathway. No inherited disease has been attributed to germline variants in this gene. There is no ClinVar entry, no ClinGen assessment, and no GeneReviews chapter. The clinical significance of your variant is currently unknown.

GENE EXPRESSION

Most active in: Colon, Pancreas, Kidney, Testis, Lung

WHAT THIS MEANS FOR YOU

You carry a frameshift variant in SMIM22, a gene that makes a small membrane protein involved in regulating lipid droplets, the cell's fat-storage compartments, likely through an interaction with SQLE, a cholesterol-pathway enzyme. Your variant probably causes this one copy to produce little or no functional protein. Because inheritance is thought to be autosomal recessive, your second copy is unaffected and expected to maintain normal function. No clinical syndrome has been linked to inherited SMIM22 variants. Published studies mention this gene only in tumour tissue expression data, which cannot predict your personal health risk. This variant is currently a finding of uncertain significance with no established consequence for your daily life.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Loss-of-function, no known disease

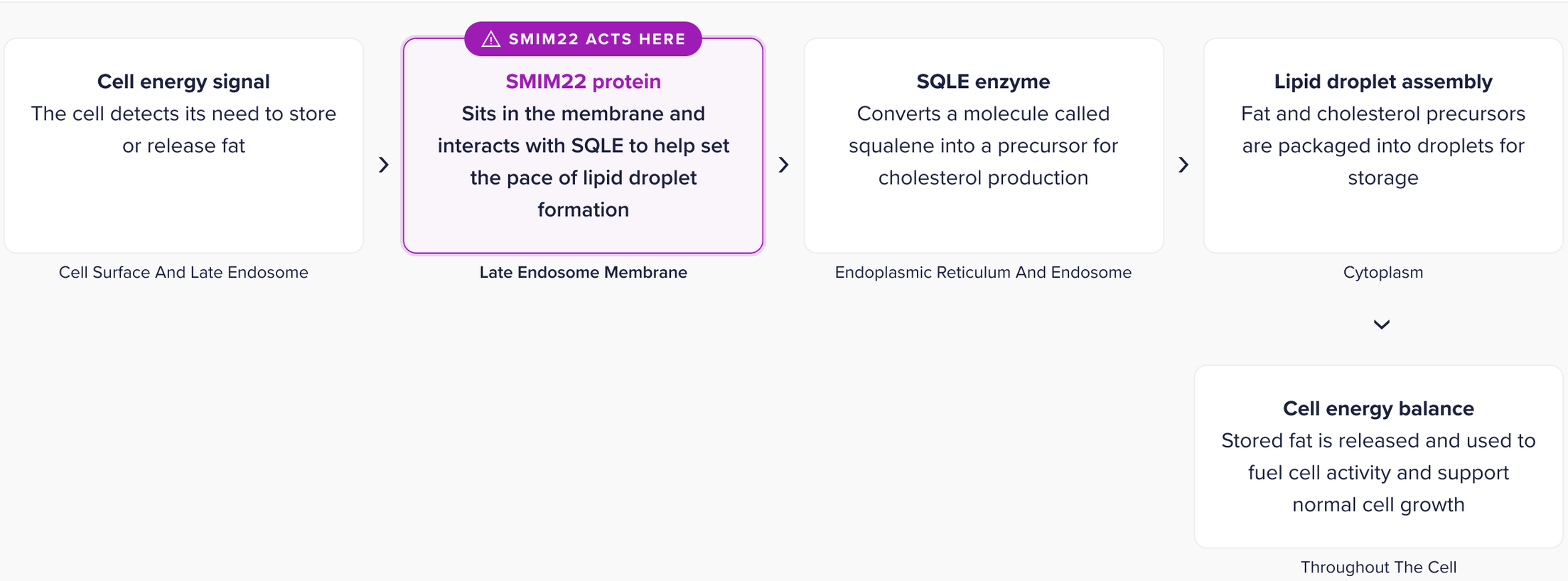
SMIM22 encodes a small protein embedded in cell membranes, located in late endosomes. Its documented role is helping to regulate lipid droplet formation, the cell's fat-storage compartments, likely through interaction with SQLE, a key enzyme in the cholesterol synthesis pathway. No Mendelian disease has been linked to germline variants in this gene.

Your variant, p.Thr43SerfsTer27, is a frameshift that introduces a premature stop signal and likely reduces functional SMIM22 protein from this one copy. Because no clinical syndrome has ever been defined for germline variants in SMIM22, this finding cannot be counselled as a recognised disease. The available literature describes SMIM22 mRNA changes in tumour tissue only. Those are somatic, in-tumour observations and cannot be used to predict your personal risk. Your other copy of this gene is unaffected. At this time, this variant is a finding of unknown clinical significance, and no management changes are indicated on the basis of it alone.

LIPID DROPLET REGULATION VIA SQLE INTERACTION

Why this matters: The only documented molecular function of SMIM22 is its potential role in controlling how cells form lipid droplets through interaction with SQLE. This is the most grounded picture available of what reduced SMIM22 activity might mean at the cellular level.

Your cells constantly make and store small parcels of fat called lipid droplets. Think of these as the cell's pantry. SQLE is a key worker in the cholesterol-making production line. SMIM22 appears to act as a regulating signal, sitting in the membrane and influencing how much fat gets packaged into those droplets. When SMIM22 function is reduced, that regulatory signal may be altered.



When this pathway is impaired:

With reduced SMIM22 function from this copy, the regulatory input on lipid droplet formation may be diminished. The precise downstream effect in humans is not yet established.

SPATA31C1

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Spermatogenesis	INFORMATIVE	9-87915586-87919008-C-<DEL>-DEL	NP_001138596.1:1/4	N/<DEL>	High Impact

SPATA31C1 is what scientists call a pseudogene — a retired copy of an older, once-active gene. The gene family it descends from may have helped with sperm production and UV-damaged DNA repair, but SPATA31C1 itself no longer makes a working protein. You have a deletion removing one of your two copies of this locus. Because no functional protein is expected and no recognised medical condition has been linked to changes here, this finding does not currently point to a known health problem.

GENE EXPRESSION

Most active in: Testis | Kidney | Liver | Lung | Colon

WHAT THIS MEANS FOR YOU

You have a deletion affecting one of your two copies of SPATA31C1. This gene is a pseudogene, essentially a dormant genomic remnant that no longer makes a working protein. Think of it as a faded, unreadable copy of an old instruction manual. Losing one copy does not remove any known protein from your body and is not linked to any recognised inherited condition. One early computational study noted its RNA levels were altered in some cancers, but that does not mean this deletion raises your cancer risk. There is no documented clinical effect of carrying one deleted copy, and no established symptoms or triggers are associated with this finding. Right now, this is a variant of uncertain meaning, not a diagnosis.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Head and Neck Cancer (pseudogene expression association)

Head and neck cancer is a broad term covering malignancies of the mouth, throat, voice box, salivary glands, and nearby structures. These cancers vary widely in their causes and outcomes, and overall survival has remained around 50% for decades. Researchers are actively investigating molecular markers, including pseudogene RNA transcripts, that may help predict susceptibility or prognosis.

Your deletion removes one copy of the SPATA31C1 locus. The only published evidence connecting this gene to cancer is a single in-silico study that found SPATA31C1 transcript levels to be among the most deregulated pseudogene signals in head and neck cancer samples, with higher or lower expression correlating with patient survival (PMID: 34440428). Crucially, that study analysed tumour tissue expression patterns. It did not study germline deletions like yours, and it measured no direct cause-and-effect relationship. There is currently no evidence that having one deleted copy of this locus in your normal cells meaningfully raises your personal risk of head and neck cancer. This association is a research-stage observation, not a clinical risk finding you need to act on today.

Spermatogenesis-related function (pseudogene family context)

Spermatogenesis is the process by which the body produces sperm. The SPATA31 gene family, of which SPATA31C1 is a pseudogene member, has been linked to this process. Disruptions in related family members have been investigated in the context of male fertility, though no Mendelian infertility syndrome has been formally attributed to SPATA31C1 itself.

Because you are male, the testis-predominant expression of the SPATA31 gene family is worth noting. However, SPATA31C1 itself is annotated as a pseudogene. It does not produce a functional protein, and no study has documented that a heterozygous deletion of this specific locus causes infertility or reduced sperm quality. If fertility is a concern for you, a standard semen analysis through your doctor is the appropriate next step, since it would detect any actual sperm abnormality far more directly than this genetic finding can.

PSEUDOGENE RNA REGULATION

Why this matters: SPATA31C1 has no curated biological pathway because it does not produce a working protein. The only scientifically noted activity is that its RNA transcript may influence nearby gene activity, making this speculative regulatory role the most relevant frame for understanding your variant.

Most genes work like a recipe card: the gene is the card, the finished dish is the protein. Pseudogenes are like worn-out photocopies of old recipe cards where the instructions have faded beyond use. They cannot produce a dish on their own. Scientists are now asking whether these faded cards might still do something in the kitchen, but that idea is not yet proven for SPATA31C1.

SPATA31C1 gene locus
The cell reads the DNA at this location and produces an RNA molecule

Cell Nucleus

⚠ SPATA31C1 ACTS HERE

SPATA31C1 RNA transcript
The RNA is released into the cell but, unlike most genes, it does not carry a complete blueprint for making a protein

Cell Nucleus And Cytoplasm

Nearby gene regulators
The RNA may interact with molecules that control nearby genes, potentially nudging how active those genes are

Cytoplasm

Cell behaviour
Any downstream effect on cell growth or stress response would emerge here, but this chain of events is not yet established for SPATA31C1

Whole Cell

When this pathway is impaired:

With one copy deleted, any regulatory RNA this locus produces may be reduced. Whether that has any practical health consequence is not currently known.

TAS2R19

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Bitter taste perception	INFORMATIVE	rs777991764	NP_795369.1:p.Arg210AlafsTer4	G/GC	High Impact

VARIANT POPULATION FREQUENCY: 2/100,000

TAS2R19 is one of roughly 25 bitter taste receptor genes in the human genome. It sits on the surface of taste cells on your tongue and acts as a sensor for bitter-tasting molecules, particularly compounds found in grapefruit. Beyond taste, the receptor is also found in tissues like the lung, colon, and testis, suggesting it may sample the chemical environment inside the body. No recognised clinical disease is linked to variants in this gene, and your finding does not point to any health condition requiring monitoring or treatment.

GENE EXPRESSION

Most active in: Testis · Pancreas · Colon · Lung · Kidney

WHAT THIS MEANS FOR YOU

You have one altered copy of TAS2R19, a gene that produces a receptor helping you detect bitter flavours, especially those in grapefruit. Because this gene follows an autosomal recessive pattern, your one fully working copy is sufficient to maintain normal receptor function. At most, you might perceive certain bitter compounds very slightly differently than someone with two fully working copies, though even this subtle effect has not been firmly proven for loss-of-function variants. No clinical condition or health risk has been linked to having one altered copy of TAS2R19. This finding requires no changes to your diet, medications, or medical care.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

sensory perception of bitter taste

The ability to detect bitter-tasting compounds depends on a family of specialised receptors on taste cells. When these receptors function differently, the intensity or quality of bitter flavours, such as the bitterness in grapefruit juice or tonic water, may be perceived differently from person to person.

You have one working copy and one non-working copy of TAS2R19. Because this gene follows an autosomal recessive pattern, one working copy is generally sufficient to maintain receptor activity. The practical result, if any, is a subtle and likely unnoticeable shift in how intensely you perceive certain bitter flavours, particularly grapefruit-type bitterness. Even that modest effect is not firmly established for loss-of-function variants specifically. Published taste associations involve a common missense variant (rs10772420), and one study found that associations may actually reflect a nearby gene, TAS2R31, rather than TAS2R19 itself (PMID: 26024668). No health consequence is linked to this finding.

chronic rhinosinusitis

Chronic rhinosinusitis is a long-term inflammation of the sinuses and nasal passages lasting twelve weeks or more. It causes nasal congestion, facial pressure, reduced sense of smell, and nasal discharge, and can significantly affect quality of life.

TAS2R19 is expressed in airway tissue, and bitter taste receptors in the sinuses have been studied for a possible role in sensing bacterial molecules and triggering local defence responses. However, the OpenTargets association score for TAS2R19 and chronic rhinosinusitis is very low (0.01), and no study has linked heterozygous loss-of-function variants in TAS2R19 specifically to an increased risk of sinus disease. This association is exploratory and does not warrant any change to your current care.

breast carcinoma

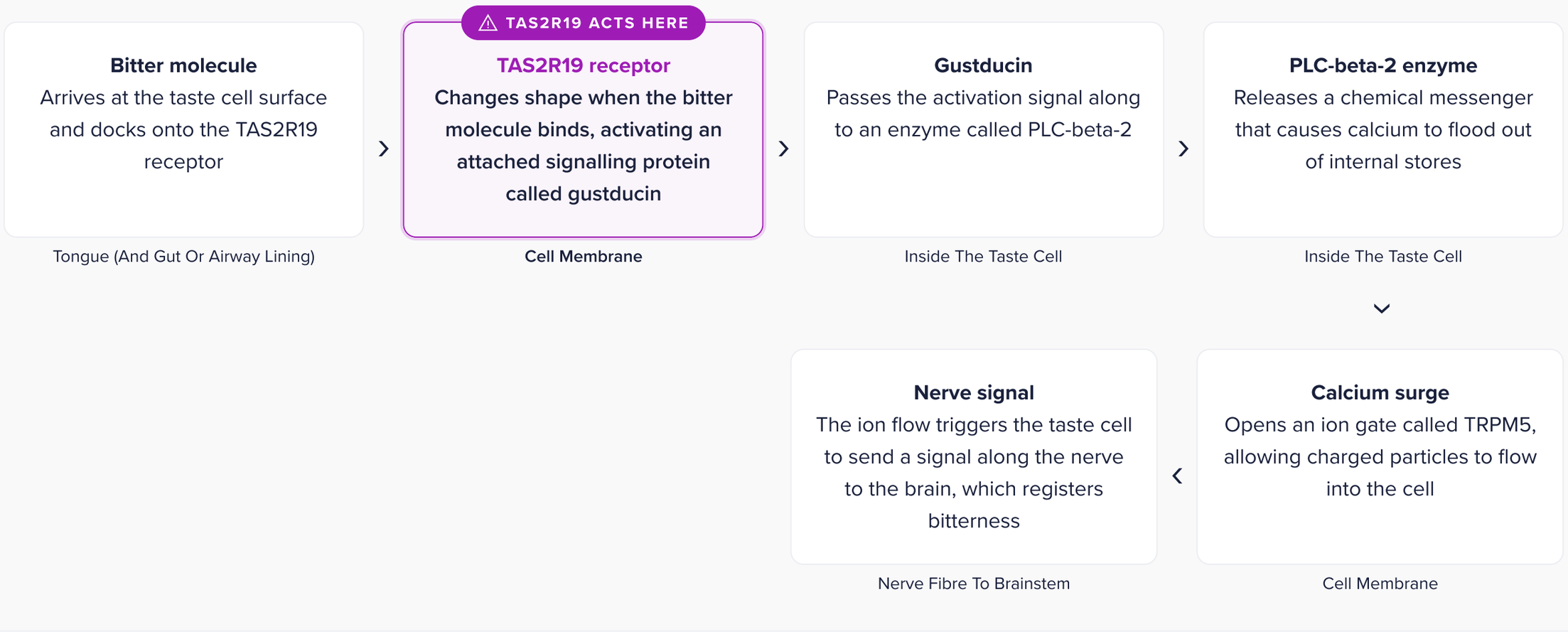
Breast carcinoma is a malignant tumour arising from breast tissue. It is one of the most common cancers globally and can vary widely in behaviour, from slow-growing to aggressive forms.

The OpenTargets association between TAS2R19 and breast carcinoma carries a score of only 0.04 and is not supported by any established biological mechanism or clinical study linking this gene's loss of function to breast cancer risk. As a male, your baseline risk of breast cancer is already very low. This weak statistical signal does not change your screening recommendations and requires no action.

BITTER TASTE SIGNALLING

Why this matters: This pathway shows how your tongue (and possibly other tissues) detects bitter molecules and converts that detection into a nerve signal. It is the central process affected by your TAS2R19 variant, and understanding it makes clear why the effect is limited to taste perception rather than a broader health function.

Think of TAS2R19 as a doorbell on the surface of a taste cell. A bitter molecule rings the doorbell, triggering a chain of messengers inside the cell that eventually opens a tiny gate, letting charged particles flood in and fire a nerve signal to the brain. With one working doorbell and one broken one, the overall signal is likely modestly reduced but not absent.



When this pathway is impaired:

One of your two TAS2R19 doorbells is broken, so the first detection step may fire less reliably. The remaining working copy still functions, but the bitterness signal from this receptor may be modestly reduced.

TMEM59

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Cellular self-cleaning	INFORMATIVE	rs200790405	Altered protein assembly	C/T	High Impact

VARIANT POPULATION FREQUENCY: 2/10,000

TMEM59 makes a protein in the Golgi (your cell's sorting office), endosomes, and lysosomes (the recycling bins). It has two jobs: guiding how proteins are sugar-coated and shipped, and triggering cellular self-cleaning (autophagy). You carry one altered copy alongside one fully working copy. No Mendelian disease is linked to heterozygous loss of TMEM59. Mouse research hints that reduced TMEM59 activity may mildly protect against Alzheimer-type amyloid build-up, but this is unconfirmed in humans.

GENE EXPRESSION

Most active in: Pancreas | Liver | Colon | Kidney | Lung

WHAT THIS MEANS FOR YOU

You carry one altered copy of TMEM59, with the other copy working normally. Because this gene follows an autosomal recessive pattern, having one altered copy is not expected to cause any health condition, and no clinical syndrome has been linked to this situation in humans. Intriguingly, mouse studies found that reduced TMEM59 dosage slowed amyloid-beta plaque build-up and improved memory in an Alzheimer model, and a 2024 review described this as potentially neuroprotective. These are animal findings not confirmed in people, so they carry no health recommendation. The most practical use of this result today is for family planning: each biological child you have has a 50% chance of inheriting this variant.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Alzheimer disease

Alzheimer disease is a progressive neurodegenerative condition that gradually impairs memory, thinking, and daily functioning. It is the most common cause of dementia and is driven, in part, by the accumulation of amyloid-beta plaques and tau tangles in the brain.

TMEM59 helps keep a protein called APP parked inside the cell's processing hub (the Golgi) rather than moving to the cell surface, where it would be cleaved into amyloid-beta, the sticky fragment that builds up in Alzheimer's disease (PMID: 20427278). You carry one altered and one fully working copy of the gene. Perhaps surprisingly, mouse studies found that reduced TMEM59 dosage, exactly the situation your variant creates, actually produced fewer amyloid plaques and rescued memory performance in an Alzheimer model (PMID: 33195275). A 2024 review echoed this, listing TMEM59 haploinsufficiency among factors that may slow amyloid deposition (PMID: 39596030). These are animal findings and have not been confirmed in human cohort studies, so they cannot be translated into a personal risk estimate. The gene also tolerates loss-of-function variation well in the general population, and no human clinical syndrome has been linked to carrying one altered TMEM59 copy. This result does not change your Alzheimer disease risk management compared to anyone else, and the prevailing animal evidence points toward a neutral-to-protective effect at your zygosity, not an increased risk.

Estrogen resistance syndrome

Estrogen resistance syndrome is a rare condition in which cells fail to respond normally to estrogen signalling, leading to disrupted metabolic, skeletal, and reproductive processes despite normal or elevated estrogen levels in the blood.

TMEM59 appears as the top computational association for estrogen resistance syndrome in the OpenTargets database, with a score of 0.18. This is a statistical signal, not a finding from any genetic study linking TMEM59 variants to this condition in humans. No peer-reviewed literature reviewed here describes a causal or mechanistic connection between TMEM59 and estrogen signalling. This association is not clinically meaningful for you at this time and does not require any action.

Ischemic stroke

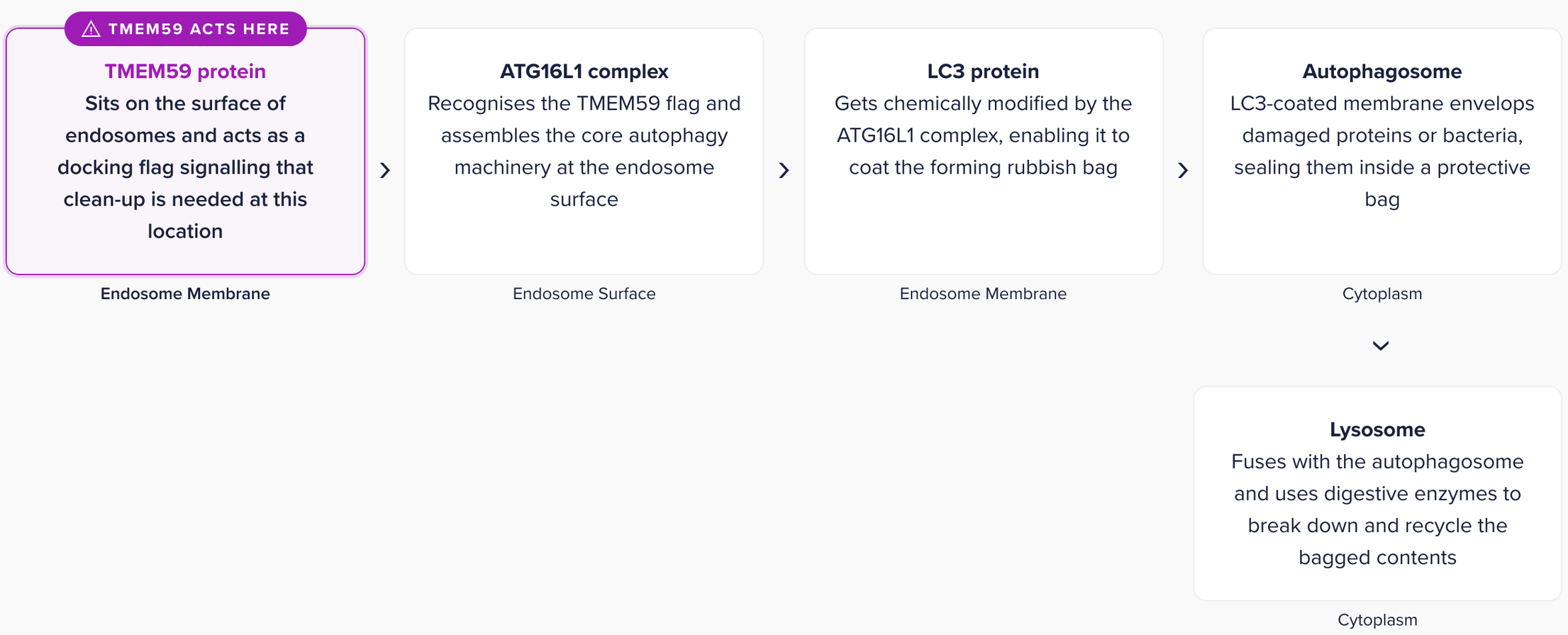
Ischemic stroke occurs when a blood clot blocks an artery supplying the brain, cutting off oxygen and causing rapid death of brain tissue. It is a leading cause of disability and death worldwide.

Mouse studies found that complete removal of both copies of TMEM59 worsened outcomes after ischemic stroke, increasing infarct volume and amplifying microglial inflammation through the NLRP3 and NF-kB pathways (PMID: 33517129). You carry one fully working copy of TMEM59, which is a fundamentally different situation from having both copies knocked out. No human evidence connects heterozygous TMEM59 loss-of-function to elevated stroke risk. Standard cardiovascular risk factor management, including healthy blood pressure, avoiding smoking, staying physically active, and a heart-healthy diet, remains the appropriate guidance and is not altered by this variant.

THE CELLULAR SELF-CLEANING (AUTOPHAGY) PATHWAY

Why this matters: Autophagy is how your cells recognise damaged or dangerous material, wrap it up, and send it for recycling. TMEM59 acts as the docking flag that tells the autophagy machinery where to start. This pathway is the primary mechanistic basis for TMEM59's known biological function.

Think of autophagy as your cell's rubbish-collection service. Certain proteins on the cell's internal membranes act like a bin-lorry call button. TMEM59 is one of those buttons: when pressed, it recruits the team that wraps rubbish in a bag and drives it to the recycling centre. With one altered copy of TMEM59, the button works less often, so some cellular waste may take longer to be cleared.



When this pathway is impaired:

With reduced TMEM59 signalling, the call to start the clean-up is weaker. Some damaged proteins or intracellular bacteria may linger longer before being cleared.

TPSB2

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Immune signaling	INFORMATIVE	rs782257892	NP_077078.5:p.Met153AspfsTer14	C/CG	High Impact

VARIANT POPULATION FREQUENCY: 12/100

TPSB2 carries the instructions for making tryptase beta 2, an enzyme packed inside your mast cells — the immune sentinels scattered throughout your skin, gut, and lungs. When a mast cell is triggered by an allergen, an infection, or tissue damage, it releases tryptase to help coordinate inflammation and wound healing. You have one altered copy of this gene. The reviewed literature does not link this to any defined clinical condition, and the gene's population constraint data confirm that one disrupted copy is well tolerated.

GENE EXPRESSION

Most active in: Lung | Colon | Pancreas | Kidney | Liver

WHAT THIS MEANS FOR YOU

You carry one working and one altered copy of TPSB2, which makes beta-tryptase, a key enzyme mast cells release during immune responses. Because this gene follows a recessive pattern, one altered copy is not expected to cause any health problems. Your second intact copy, plus the related gene TPSAB1, keeps supplying beta-tryptase. No clinical symptoms have been documented at this zygosity. If tryptase is ever measured in a blood test, it may read slightly low, which is benign. The main relevance is family planning: if a future partner also carried a TPSB2 loss-of-function variant, each pregnancy would carry a 1-in-4 chance of two non-working copies, though no clinical syndrome for that scenario has been documented.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Urticaria

Urticaria, commonly called hives, is a skin condition characterised by raised, itchy welts that appear when mast cells release histamine and other immune chemicals into the skin. Episodes can be acute (lasting less than six weeks) or chronic, and they range from mildly annoying to significantly disruptive.

TPSB2 appears in the top associations for urticaria with a modest score of 0.32, reflecting its role as a mast cell activity marker rather than a proven causal gene. You carry one working copy and one altered copy of TPSB2. Because TPSB2 follows an autosomal recessive inheritance pattern and its constraint scores (pLI ~0.001, LOEUF ~1.04) show the gene is broadly tolerated across the population, carrying one reduced-output copy does not establish a documented personal risk for urticaria. As a heterozygous carrier, your own risk of developing any TPSB2-related illness is very low. No published study has shown that people with one non-working TPSB2 copy develop urticaria or any other mast-cell condition at higher rates than the general population. (PMID: 34400315, PMID: 34175497)

Immunodeficiency due to a late component of complements deficiency

Deficiencies in the late complement components (C5 through C9) impair the immune system's ability to form the membrane attack complex, leaving the body less able to clear certain encapsulated bacteria, particularly Neisseria species, and raising susceptibility to meningococcal disease.

This association appears in the OpenTargets data for TPSB2 at a low score of 0.09, most likely because tryptase participates broadly in innate immune signalling rather than because TPSB2 loss directly causes complement deficiency. There is no published evidence linking one reduced-function TPSB2 copy to complement component deficiency in humans. Your heterozygous status at an autosomal recessive gene with very permissive constraint scores does not support any meaningful personal risk here based on current literature. If you ever experience recurrent serious bacterial infections, that would warrant evaluation through separate clinical routes unrelated to this variant. (PMID: 34400315)

Chronic mucocutaneous candidosis

Chronic mucocutaneous candidiasis is a rare immune disorder in which persistent or recurrent Candida fungal infections affect the skin, nails, and mucous membranes. It is typically caused by defects in T-cell-mediated or innate immune pathways and usually presents in childhood.

TPSB2 carries a low OpenTargets association score of 0.08 for this condition, reflecting tryptase's general role in innate immunity rather than a specific causal link. No published literature documents that carrying one non-working copy of TPSB2 increases risk for chronic mucocutaneous candidiasis. Your heterozygous status at this autosomal recessive, population-tolerant gene is not currently considered clinically relevant to this condition. (PMID: 34175497)

Mendelian susceptibility to mycobacterial diseases due to complete IFNgammaR2 deficiency

This rare primary immunodeficiency is caused by complete loss of the interferon-gamma receptor 2 (IFNgammaR2), which severely impairs the body's ability to fight mycobacterial infections such as tuberculosis and non-tuberculous mycobacteria. It typically presents in early childhood with severe, recurrent, or disseminated mycobacterial disease.

This condition is listed in the OpenTargets data for TPSB2 at a very low score of 0.07, and no published study connects a heterozygous TPSB2 loss-of-function variant to IFNgammaR2 deficiency or mycobacterial susceptibility. The association almost certainly reflects broad mast-cell immune network co-expression data rather than a causal relationship. Your one altered TPSB2 copy has no documented impact on this pathway. (PMID: 34400315)

MAST CELL ALARM AND REPAIR PATHWAY

Why this matters: When your immune system encounters a threat, mast cells act as first responders by releasing tryptase beta 2. Understanding this pathway explains what the enzyme normally does and why one reduced-output copy has limited consequences for you.

Think of a mast cell as a pre-loaded fire-alarm station sitting in your tissues. When it detects danger, it fires off a burst of chemicals including tryptase, which spread the alarm to nearby cells and help start the repair process. Your altered copy means one of your two TPSB2 stations has reduced output, but the other copy and the closely related gene TPSAB1 continue producing tryptase, so the alarm system still functions.

Mast cell
Sits quietly in tissues loaded with packets of tryptase and other alarm chemicals, ready to respond

Skin, Gut, And Lung Tissue Barriers

›

Trigger signal
An allergen, pathogen, or tissue injury activates the mast cell surface, telling it to fire

Cell Surface

›

⚠ TPSB2 ACTS HERE

Tryptase beta 2 (TPSB2)
Stored packets of tryptase are released into the surrounding tissue as the mast cell degranulates; your altered copy produces less of this protein

Secretory Granules, Then Outside The Cell

›

Tryptase tetramer
Four tryptase molecules join together to form the active, working enzyme that can act on targets

Extracellular Space

Repair signals
Tryptase also triggers wound-healing processes, helping tissue recover after the threat has passed

Tissue

‹

Nearby immune cells
Active tryptase binds to neighbouring cells, amplifying the inflammatory signal and recruiting more immune cells to the site

Tissue

When this pathway is impaired:

One TPSB2 copy produces less functional tryptase, but the second copy and TPSAB1 continue supplying the enzyme, so the overall alarm-and-repair system is not clinically disrupted.

TPTE

⊘ LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Cell signal tuning	INFORMATIVE	21-10511076-10623497-A-<DEL>-CNV	NP_954870.3	N/<DEL>	High Impact

TPTE is a membrane protein expressed almost exclusively in the testis, thought to fine-tune chemical signals involved in cell growth. A key quirk: your genome normally contains multiple near-identical backup copies on other chromosomes, so losing one copy from chromosome 21 does not eliminate all TPTE activity. No inherited disease has been formally linked to germline TPTE deletion, and no clinical management guidelines exist. The evidence here is genuinely limited.

GENE EXPRESSION

Most active in: Testis · Lung · Kidney · Colon · Liver

WHAT THIS MEANS FOR YOU

You carry one deleted copy of TPTE on chromosome 21, while your other copy is intact. TPTE helps fine-tune chemical signals inside cells and is most active in the testis during sperm formation. Crucially, your genome also holds several near-identical TPTE copies on other chromosomes that may largely compensate for the deleted one. No clinical syndrome has been linked to having one altered copy, and no established symptoms or health risks apply here. This variant is informational rather than a cause for concern. If future family planning is on your mind, it is worth mentioning this result to your doctor given TPTE's role in sperm-forming cells, though no human study has confirmed that germline loss affects fertility.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

Loss-of-function variant in TPTE, no known disease association

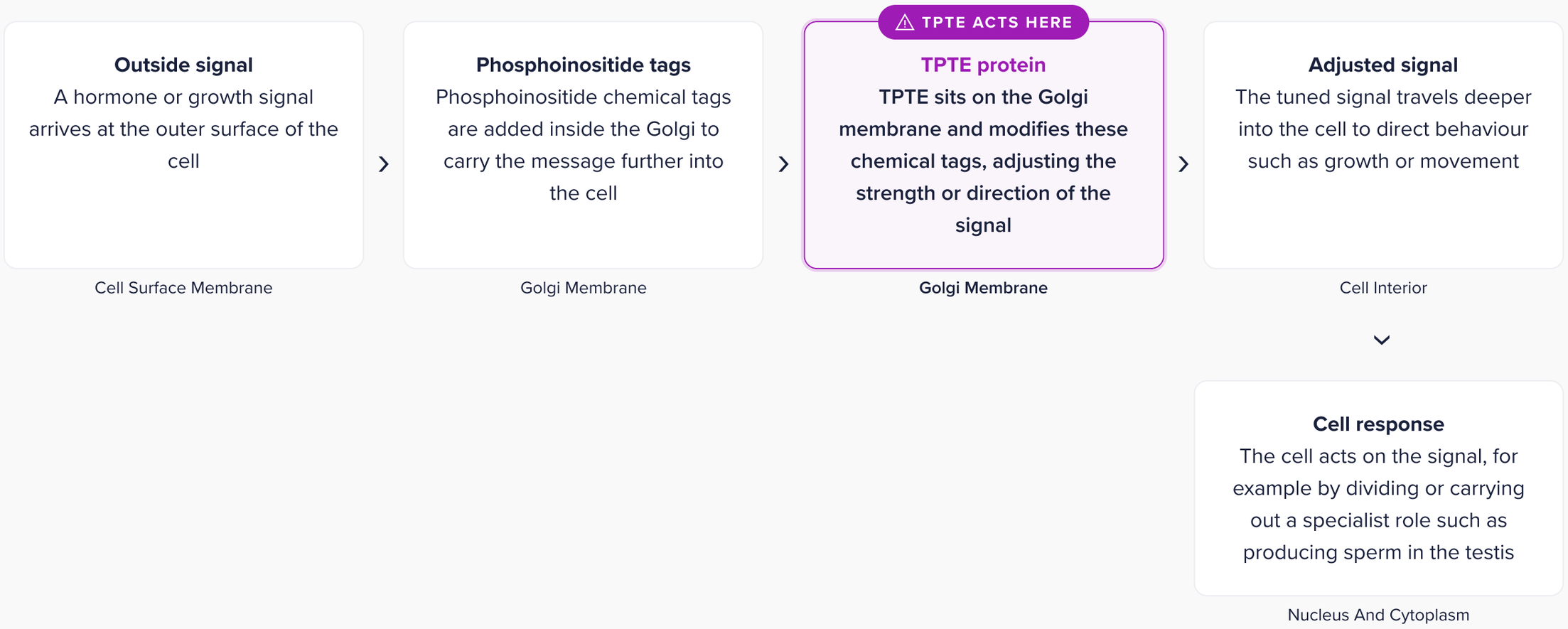
TPTE encodes a membrane-bound protein expressed most highly in the testis, where it is thought to help fine-tune internal cell signalling involving phosphoinositide lipid tags. Despite having a recognisable phosphatase domain, its enzymatic activity and precise biological role have not been fully established, and no recognised Mendelian disease has been linked to germline changes in this gene.

You carry one deleted copy of TPTE on chromosome 21 alongside one intact copy. The current medical literature does not describe any clinical syndrome arising from having one non-working copy of this gene. Importantly, the human genome contains five to seven near-identical copies of TPTE spread across chromosomes 13, 15, 22, and Y, meaning your remaining copies may partially compensate for the deleted one. This variant sits in the 'no known disease' category today, which is genuinely reassuring. It also means there is no established playbook of symptoms to watch for or precautions to take. The most credible area of biological interest, given that TPTE is expressed in sperm-forming cells, is a possible contribution to male fertility, but no human study has confirmed that germline TPTE loss causes infertility. It is worth mentioning this finding to your doctor if fertility is a consideration for you now or in the future. No special monitoring, medication restrictions, or dietary changes are indicated based on current evidence.

PHOSPHOINOSITIDE SIGNAL TUNING AT THE GOLGI MEMBRANE

Why this matters: TPTE sits on the Golgi membrane and modifies phosphoinositide molecules that relay growth signals inside cells. Understanding this pathway explains TPTE's normal job and why its disruption is hard to predict without more research.

Inside every cell there is an internal sorting station called the Golgi. Cells use small chemical tags called phosphoinositides as internal sticky notes carrying messages like 'keep growing' or 'slow down'. TPTE sits on this station and reshapes those sticky notes, fine-tuning the message. When this works correctly, cells respond proportionately to signals from outside.



When this pathway is impaired:

With reduced TPTE activity, fine-tuning of phosphoinositide signals at the Golgi may be impaired, but the real-world consequence in people with one working copy is not yet established.

ZNF425

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Gene activity control	INFORMATIVE	rs769014744	NP_001001661.1:p.Lys518ThrfsTer51	GACCT/G	High Impact

VARIANT POPULATION FREQUENCY: 4/100,000

ZNF425 acts as a molecular dimmer switch, turning down specific genes during the earliest months of embryonic development, notably in the heart. It also helps keep repetitive DNA sequences silenced. Your variant truncates the protein from one copy of the gene, likely reducing repressor function from that copy. No established clinical disease has been linked to ZNF425 loss-of-function in current medical literature, so the health meaning of your variant is not yet known.

GENE EXPRESSION

Most active in: Colon, Kidney, Pancreas, Testis, Liver

WHAT THIS MEANS FOR YOU

You carry one altered copy of ZNF425, a gene whose protein acts like a volume knob during early development, quietly turning off certain genes at the right time. Your variant causes that one copy to produce a shorter, likely non-functional protein. Your other copy still works normally. No clinical syndrome or health risk has been linked to having one altered copy of this gene in any published research. Weak database signals hint at possible connections to conditions like proptosis, but these are unconfirmed. This is a variant of uncertain significance: it tells us something about your DNA, but not yet what it means for your health. Nothing about your daily life needs to change based on this result today.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

ZNF425 loss-of-function variant of uncertain clinical significance

ZNF425 encodes a KRAB zinc finger protein that acts as a transcriptional repressor, most active during early embryonic development. It helps silence certain genes and regulate a signalling pathway (MAPK) involved in cell growth. Its precise role in human disease has not yet been established.

You have one working copy and one truncated, likely non-functional copy of ZNF425. Because no clinical syndrome has been linked to loss-of-function variants in this gene in any published case series or disease registry, this finding does not correspond to a diagnosis. The inheritance pattern is listed as autosomal dominant, but whether a single altered copy actually causes health problems is entirely unknown at this stage. Large database signals weakly mention proptosis and neurodegenerative disease, but these are very low-confidence statistical associations, not confirmed conditions. You should not treat this as a diagnosis. If research advances, your clinical team can revisit this variant.

GENE ACTIVITY CONTROL DURING EARLY DEVELOPMENT

Why this matters: ZNF425 sits at a control point where a growing embryo decides which genes should stay quiet. It does this partly by dampening a major growth-signal relay called the MAPK pathway. Understanding this helps explain what having one altered copy of ZNF425 could theoretically mean, even though no clinical outcome has been confirmed in the literature.

Think of your DNA as a huge music playlist. ZNF425 is a specific mute button that keeps certain tracks silent during early development. It also acts as a brake on a busy internal messaging system (MAPK) that tells cells to grow and divide. Your other, working copy of ZNF425 is still pressing that button.

When this pathway is impaired:

With one altered copy, the repressor mute button may be less effective, though your remaining working copy still provides repressor activity. No confirmed clinical consequence has been documented.

KEY ACTIONS

There is no specific action required right now. Let your primary care doctor or a genetics specialist know this variant was found so it can be noted in your medical record. If future research establishes a clear disease link for ZNF425 loss-of-function variants, your clinical team can reassess. No dietary, exercise, medication, or supplement changes are indicated based on current evidence.

ZNF440

LOSS-OF-FUNCTION

FUNCTION	STATUS	VARIANT	PROTEIN / EFFECT	GENOTYPE	IMPACT ON GENE
Gene regulation	INFORMATIVE	rs200705543	NP_689570.2: p.Arg412Ter	C/T	High Impact

VARIANT POPULATION FREQUENCY: 5/1,000

ZNF440 encodes a zinc finger protein that lives inside the nucleus of your cells and acts as a gene-regulation switch, binding directly to DNA to help turn other genes on or off. Your variant introduces a premature stop signal in one of your two copies, likely reducing the functional protein that copy produces. However, ZNF440 is not currently linked to any recognised hereditary condition, and what a single altered copy means for your personal health is genuinely unclear based on today's evidence.

GENE EXPRESSION

Most active in: Colon Lung Testis Pancreas Kidney

WHAT THIS MEANS FOR YOU

You carry one altered copy of ZNF440, a gene that helps control which other genes get switched on or off in your cells. Because this variant follows an autosomal recessive pattern, your second working copy continues doing the job normally. No health condition caused by a single altered copy has been described, so your personal risk from this variant alone is not established. It is most relevant to family planning: if a future partner also carried a ZNF440 variant, each pregnancy would have a 1-in-4 chance of inheriting both altered copies. Even that scenario has no formally defined syndrome. This finding is informational today, not a cause for concern.

ASSOCIATED CONDITIONS

Association research shows a connection (an association) between this gene and the condition, but it does not mean the variant causes the condition. Genetic variants usually only account for a very small part of your overall risk, because many other genes and lifestyle factors play a role in developing most conditions. Therefore, simply having this genetic marker does not necessarily mean you are at increased risk or will develop the condition.

ZNF440-related transcriptional regulation, uncertain significance

ZNF440 is a zinc finger transcription factor that helps control which genes are switched on or off inside cells. Variants that reduce its function may subtly alter gene regulation in tissues such as cartilage, but no inherited clinical syndrome caused by ZNF440 variants has been formally described.

You carry one altered copy of ZNF440 alongside one fully working copy. Because the inheritance pattern is autosomal recessive, your single working copy continues to produce normal ZNF440 protein. No clinical syndrome from a single altered copy has been documented in the reviewed literature, and your variant is classified as Uncertain Significance with no ClinGen validity assertion or GeneReviews chapter, meaning the overall evidence base is very early-stage. The most meaningful implication right now is for family planning: if your partner also carries a loss-of-function variant in ZNF440, there would be a 1-in-4 chance with each pregnancy that a child inherits both altered copies. Even in that scenario, no defined clinical syndrome from two non-working copies has been formally described, so the health consequences would still be uncertain.

Osteoarthritis, knee (modifier association, low confidence)

Knee osteoarthritis is a degenerative joint condition in which the protective cartilage covering the ends of bones gradually breaks down, causing pain, stiffness, and reduced mobility. It is one of the most common joint conditions in adults.

The connection between ZNF440 and osteoarthritis comes from a single cell-culture study showing that higher ZNF440 activity in cartilage cells promoted breakdown of collagen and increased inflammatory enzymes (PMID: 33347923). Importantly, that research examined what happens when ZNF440 is overexpressed, not when one copy is lost. Your situation is the opposite: one altered copy producing somewhat less protein. Whether having modestly less ZNF440 activity raises or lowers any joint-related risk is genuinely unknown. The OpenTargets score for this association is very low (0.01), reflecting weak and indirect evidence. This should not be interpreted as a diagnosis or a confirmed risk factor at your zygosity.

Down syndrome (statistical association, very low confidence)

Down syndrome is a chromosomal condition caused by the presence of a full or partial extra copy of chromosome 21. It results in a range of developmental and health differences, including intellectual disability and characteristic physical features.

ZNF440 appears near a region of interest in large genomic studies of Down syndrome, but there is no established causal or modifier role for ZNF440 variants in Down syndrome risk. The OpenTargets association score is very low (0.04), reflecting statistical proximity in population data rather than a confirmed biological link. Your variant in ZNF440 does not change your personal risk of Down syndrome, which is a chromosomal condition unrelated to a single-gene loss-of-function variant.

GENE REGULATION BY ZNF440

Why this matters: ZNF440 acts as a control switch inside the nucleus, directly binding DNA to influence which genes are active. Understanding this simple on-off role explains how a change in ZNF440 could ripple outward to affect other genes in tissues such as cartilage.

Think of your DNA as an enormous instruction manual. ZNF440 is like a bookmark that tells the cell's reading machinery which pages to open and which to skip. When ZNF440 binds to a specific spot on the DNA, it encourages or discourages the cell from reading nearby genes. With one copy altered, your second, intact copy is still placing bookmarks as normal.

DNA instruction code
Sits inside the nucleus of every cell, holding the blueprints for all proteins your body makes

Cell Nucleus

›

⚠ ZNF440 ACTS HERE

ZNF440 protein
Binds to specific spots on the DNA to help control which nearby genes get switched on or off

Cell Nucleus

›

Gene-reading machinery
Responds to ZNF440's signal and either begins or holds back production of the targeted gene's protein

Cell Nucleus

›

Target gene proteins
Are produced in the right amounts at the right time, supporting cell development, tissue repair, and cartilage maintenance

Various Tissues

When this pathway is impaired:

With one copy of ZNF440 altered, the cell may have less of this regulatory switch available, potentially nudging the activity of certain target genes. The practical health consequence at the heterozygous level is not yet known.

Important Information & Disclaimer

This report was generated by SelfDecode using whole genome sequencing data. Sequencing was performed at a CAP accredited, CLIA certified laboratory (CLIA ID: 45D1102202), located at 1445 North Loop West, Suite 820, Houston, TX 77008. Laboratory Director: Dr. Feng Zhou, PhD, HCLD (ABB), CQ (NYSDOH), MB (ASCP).

This whole-genome sequencing–based screening test is intended for clinical screening purposes only and is **not a diagnostic test**. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Genetic testing is inherently complex; although uncommon, errors can result from sample mix-up, DNA contamination, or operational issues.

Reported findings reflect current detection methods, reference databases, and classification criteria. Sensitivity and specificity vary by variant type (e.g., SNVs, indels, STRs), genomic region, and sample quality. Regions of low sequence complexity, segmental duplications, or inadequate coverage may have reduced accuracy. Low-level mosaicism, large structural variants, and balanced rearrangements may not be reliably detected.

All risk estimates are approximations derived from population-based studies and may be affected by incomplete or inaccurate personal or family history information. An elevated risk result does not constitute a diagnosis and does not guarantee that a condition will develop.

Test results should be interpreted by a healthcare provider in the context of the patient's clinical presentation, medical history, and family history. **Genetic counseling is strongly recommended** to support interpretation and clinical management. Results from this screening test should not be used as the sole basis for diagnosis or treatment decisions. Confirmatory testing using alternative methodologies and a comprehensive clinical evaluation are advised when clinically indicated.

GENES ANALYZED FOR PATHOGENIC & LIKELY PATHOGENIC VARIANTS

This analysis screens all protein-coding genes in the human genome (~20,000 genes) for pathogenic and likely pathogenic variants. The following is a representative selection of clinically significant genes included in this analysis:

ABCC9, ACADM, ACADVL, ACTA2, ACTC1, AIRE, ANK2, APC, APOB, APP, ASL, ASS1, ATM, ATP7B, ATXN1, ATXN2, ATXN3, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BTD, C9orf72, CACNA1S, CALM1, CASQ2, CBS, CDH1, CDK4, CDKN2A, CFTR, CHEK2, COL1A1, COL1A2, COL2A1, COL3A1, COL4A3, COL4A4, COL4A5, CYBB, CYP21A2, CYP2C19, CYP2C9, CYP2D6, CYP3A5, DES, DMD, DMPK, DPYD, DSC2, DSG2, DSP, ELN, EMD, EPCAM, F5, F8, F9, FBN1, FGFR3, FLNA, FLNC, FMR1, FXN, G6PD, GAA, GALT, GBA1, GCDH, GJA5, GJB2, GJB6, GLA, HBA1, HBA2, HBB, HCN4, HEXA, HEXB, HFE, HMGCL, HNRNPA1, HOXB13, HTT, IDS, IDUA, IVD, KCNH2, KCNQ1, LAMP2, LDLR, LMNA, LRRK2, LZTR1, MAX, MCCC2, MCOLN1, MEN1, MLH1, MRE11A, MSH2, MSH6, MUTYH, MYBPC3, MYH7, MYH11, MYL2, MYL3, NAT2, NBN, NF1, NF2, NUDT15, OTC, PAH, PALB2, PARK7, PCCA, PCCB, PCSK9, PHEX, PINK1, PKD1, PKD2, PKP2, PLN, PMS2, PRKAG2, PRKN, PTEN, RAD51C, RAD51D, RAG1, RAG2, RB1, RET, RPE65, RYR1, RYR2, SCN1B, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SERPINA1, SERPINC1, SLC22A5, SLC25A13, SLCO1B1, SMAD3, SMAD4, SMN1, SMN2, SMPD1, SNCA, SOD1, STK11, TARDBP, TAZ, TCAP, TGFBR1, TGFBR2, TMEM43, TNNI3, TNNT2, TP53, TPMT, TRDN, TRPM4, TSC1, TSC2, TTN, TTR, UGT1A1, VHL, VKORC1, VWF, WAS, WT1, *and all other protein-coding genes*.

Please note that in rare cases, this test cannot definitively rule out the presence of pathogenic or likely pathogenic variants in any given gene. Variant interpretation depends on current scientific knowledge, database completeness, and classification criteria, all of which continue to evolve. We will update this report as new pathogenic and likely pathogenic variants are identified.

GENES ANALYZED FOR REPEAT EXPANSION

ABCD3, AFF2, AR, ARX, ATN1, ATXN1, ATXN10, ATXN2, ATXN3, ATXN7, ATXN8OS, BEAN1, C9ORF72, CACNA1A, CBL, CNBP, COMP, CSTB, DAB1, DIP2B, DMD, DMPK, EIF4A3, FGF14, FMR1, FOXL2, FXN, GIPC1, GLS, HOXA13, HOXD13, HTT, JPH3, LRP12, MARCHF6, NIPA1, NOP56, NOTCH2NLC, PABPN1, PHOX2B, PPP2R2B, PRDM12, PRNP, RAPGEF2, RFC1, RILPL1, RUNX2, SAMD12, STARD7, TBP, TCF4, THAP11, VWA1, XYLT1, ZFHX3

Please note that in some cases, the exact number of expansion repeats cannot be determined.

GENES ANALYZED FOR COPY NUMBER VARIANTS

CYP21A2, GBA, HBA1, HBA2, SMN1, SMN2

Please note that in some cases, the exact number of copy number variants cannot be determined.

SAMPLE COLLECTION & METHODOLOGY

Individual samples are self-collected using an oral swab collection device. DNA extraction is completed using magnetic bead chemistry. Library preparation is performed using Twist EF 2.0 library prep kit. Sequencing is carried out using DNBSEQ™ (DNA Nanoball Sequencing), with 2x150 paired end reads.

Genome alignment (GRCh38), variant calling, variant annotation, and variant quality filtering are performed according to internally validated pipelines following best-practice recommendations.

Variant classification is performed using an internally validated combination of tools within the Ensembl Variant Effect Predictor (VEP), publicly and privately available databases, scientific literature, and the American College of Medical Genetics and Genomics (ACMG) guidelines.

Short tandem repeat (STR) expansions were detected using ExpansionHunter. Copy number variation associated with spinal muscular atrophy was analyzed using a modified version of SMNCopyNumberCaller.

LIMITATIONS

Next-generation sequencing technology is subject to several well-characterized technical limitations. Whole-genome analysis is limited to >99% of the non-gapped DNA sequences in the human genome build GRCh38, excluding satellite DNA found in centromeres and heterochromatic regions. Although sensitivity and precision are high, there remains a small chance for false-positive and false-negative calls.

Short-Read Technology Limitations: This assay utilizes 150bp short-read sequencing. Consequently, it has inherent physical limitations in detecting complex structural variations (SVs), copy number variants (CNVs) outside the resolution of short-read depth algorithms, and repeat expansion disorders where the repeat length exceeds the 150bp read size.

High Homology & Pseudogenes: Genomic regions with high sequence homology, segmental duplications, or active pseudogenes (e.g., SMN1, CYP2D6) may yield reads that cannot be uniquely mapped by downstream informatics.

Fragmentation Bias: DNA is fragmented using enzymatic digestion (Twist EF 2.0). While optimized for uniform coverage, minor sequencing bias may occur in extreme GC- or AT-rich regions.

Sample Quality Dependency: The complexity, duplication rate, and overall uniformity of the resulting FASTQ data are highly dependent on the integrity and purity of the starting genomic DNA. Highly degraded samples (e.g., FFPE) or samples containing extraction inhibitors will exhibit suboptimal data distribution.

This data must not be used as the sole basis for clinical diagnosis, patient management, treatment decisions, or any other medical interventions. If the Customer utilizes this RUO data to develop a downstream clinical report or laboratory-developed test (LDT), the Customer bears the exclusive legal, regulatory, and ethical obligation to fully validate the entire end-to-end workflow (from raw FASTQ to final report) in a CLIA-certified and/or CAP-accredited environment before any patient results are returned.

Variants of uncertain significance (VUS) and variants with conflicting interpretations of pathogenicity are not reported.

With the exception of the genes listed below, this analysis does not detect genomic copy number variants (CNVs), including duplications or deletions above the indel size limit, whole-chromosome aneuploidy, Alu insertions, rearrangements (such as inversions and translocations), DNA methylation, or variants associated with mitochondrial-specific DNA sequences.

ExpansionHunter reliably classifies short tandem repeat expansions within its validated range, but analytical accuracy is highest for alleles up to approximately 150 base pairs (roughly 25–45 repeats). For alleles exceeding this size, precise sizing is not validated. Results are reported by expansion category rather than exact repeat numbers.

This report is for informational and educational purposes only. It is not a medical diagnosis. The interpretations and health insights in this report are not intended to diagnose, treat, cure, or prevent any disease. **Any result suggesting an elevated risk or a clinically significant variant must be confirmed by an independent CLIA-certified diagnostic test and reviewed with a qualified healthcare provider before being used to make any medical decision.**