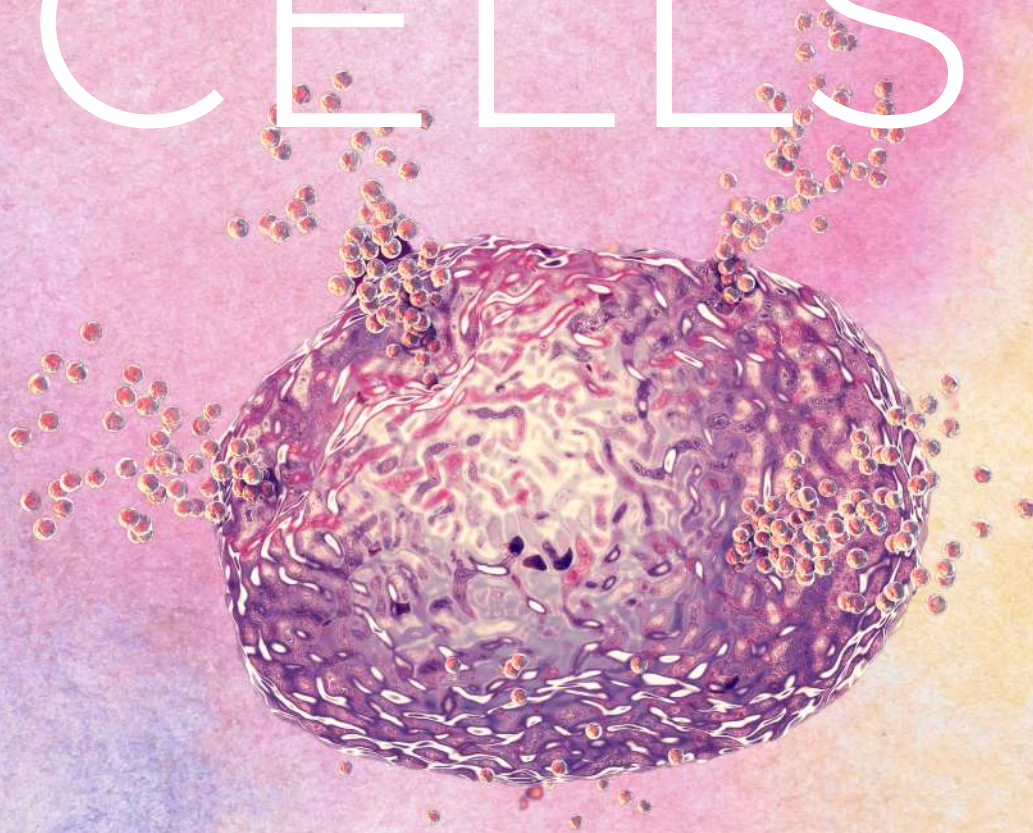


# MAST CELLS



## **Mast Cell Activation Syndrome: Genetics and Solutions**

Debbie Moon

**Genetic Lifehacks**

Learn. Experiment. Optimize.

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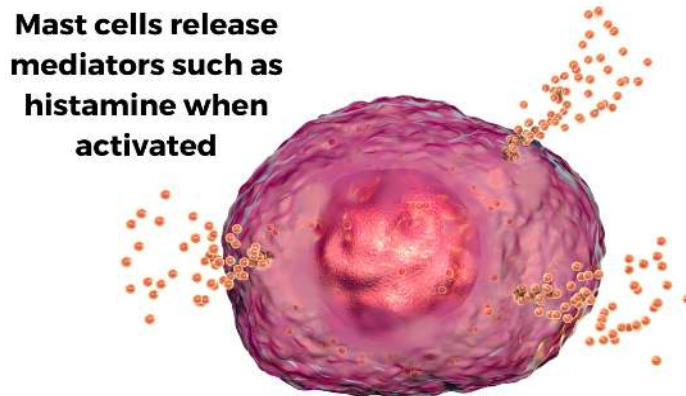
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## Introduction:

Mast Cell Activation Syndrome, or MCAS, is a recently recognized disease involving mast cells that are activated easily. Symptoms of MCAS can include abdominal pain, nausea, itching, flushing, hives, headaches, heart palpitations, anxiety, brain fog, and anaphylaxis.

This eBook explains how mast cells work and what happens when they are overactive. We will dive into some genetic factors and explore possible solutions for MCAS. All backed up by the latest research.



## What are mast cells and how do they work?

Mast cells, a type of granulocyte, contain chemicals needed in the body's immune response. These immune system cells are important for wound healing, creating new blood cells, immune tolerance, and your body's front-line defense against pathogens.

As one study summed up, mast cells are the 'jack of all trades' immune cells.

Mast cells are a part of our innate immune system and are vital to our body's response to invaders. **All good... until things go haywire.**

When mast cells trigger too easily, they degranulate and release a payload of histamine, heparin, prostaglandins, tryptase, and cytokines into the body too frequently. It causes a variety of complications with seemingly disjointed symptoms.

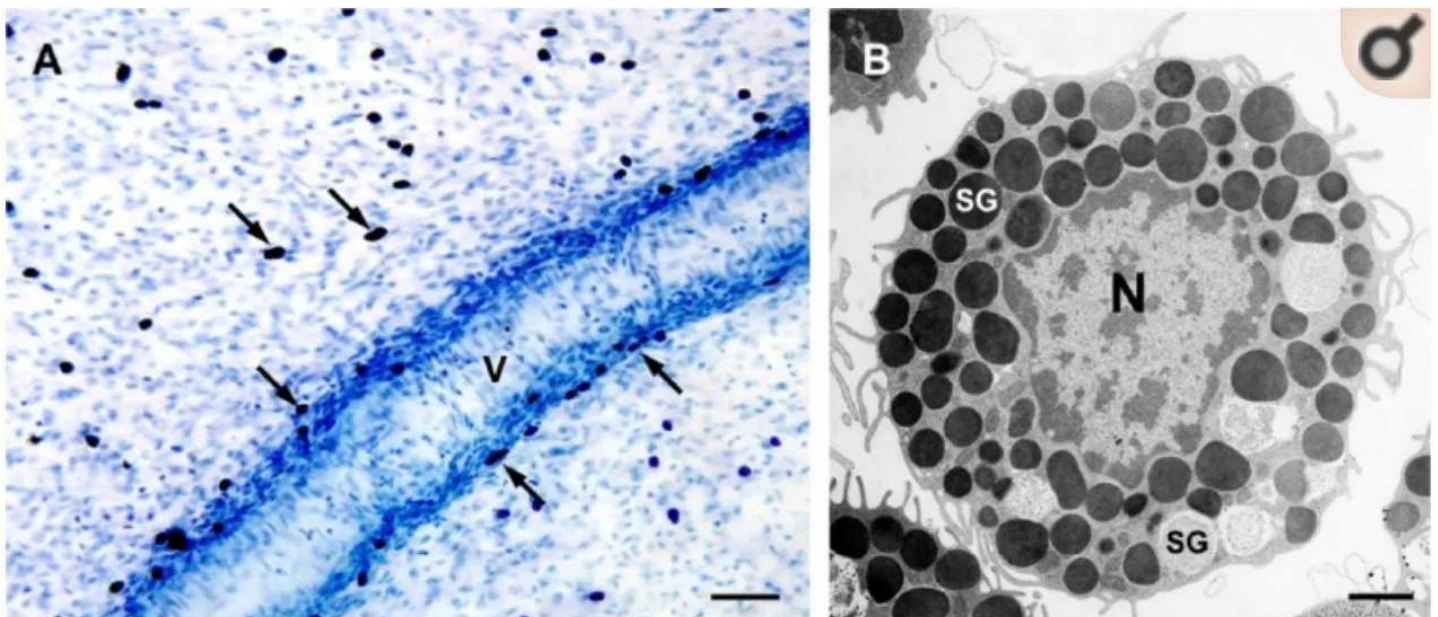
## The classic function of mast cells in the immune system:

This section will explain how mast cells usually function within the immune system (skip ahead if you already know all this...)

Mast cells are resident immune cells, meaning they aren't usually in the bloodstream but instead reside in tissue, such as connective tissue. For example, mast cells appear in the areas next to epithelial cells (skin cells, the lining of the intestines, surface cells in the lungs) or near endothelial cells, which make up blood vessels.

Granulocytes, another name for a mast cell, contain granules with several types of molecules within them. Kind of like little water balloons, mast cells can degranulate quickly — releasing various inflammatory molecules into the surrounding tissue.

Below is an image (Creative Commons License[[ref](#)]) showing the locations of mast cells along the wall of a blood vessel. The second image shows the secretory granules in a mast cell that has not been activated.



### **IgE antibodies and Immune Reactions:**

Here is a quick overview, hitting the highlights of **how mast cells respond to pathogens**:[\[ref\]](#)

Receptors known as **FcεRI receptors** are on the surface of mast cells. They bind to **IgE antibodies** created by Th2 cells and trigger B-cells to differentiate and create IgE. Usually, this happens due to a pathogen or parasite.

Once IgE has been created, it binds to the FcεRI receptor on mast cells. It **primes the mast cell** for activation as soon as the other half of the IgE binds to an antigen (on a pathogen/parasite/allergen). Called **cross-linking**, the FcεRI binds to IgE, which then binds to an antigen.

When a mast cell activates through the traditional means of an **antigen-binding to the IgE**, an immediate reaction and a delayed reaction occur.

**First:** The **immediate reaction** happens quickly, within minutes, causing the mast cell to degranulate and release its chemical-filled granules into the surrounding area.

One granule in mast cells is **histamine**, which is toxic to many parasitic organisms. Histamine, though, is more well known for its immediate cause of inflammation and allergy-type symptoms. In a nutshell, when histamine binds to histamine receptors on a cell, it causes an inflammatory immune response. For example, when histamine binds to a receptor on endothelial (blood vessel) cells, it causes vascular permeability resulting in swelling and inflammation. When histamine binds to histamine receptors on smooth muscle cells, it can cause the cells to contract. In the gastrointestinal tract, this causes vomiting and diarrhea to get rid of the pathogen. By contracting the muscles around the lungs, histamine causes coughing, sneezing, and wheezing to get rid of the pathogen.

Another component of mast cell granules are **proteases**, which break down proteins. The mast cells mainly reside in connective tissue, which has a lot of extracellular matrices made of proteins that hold the tissue together. Breaking down that extracellular matrix using proteases allows fluid to come in and flush out the body.

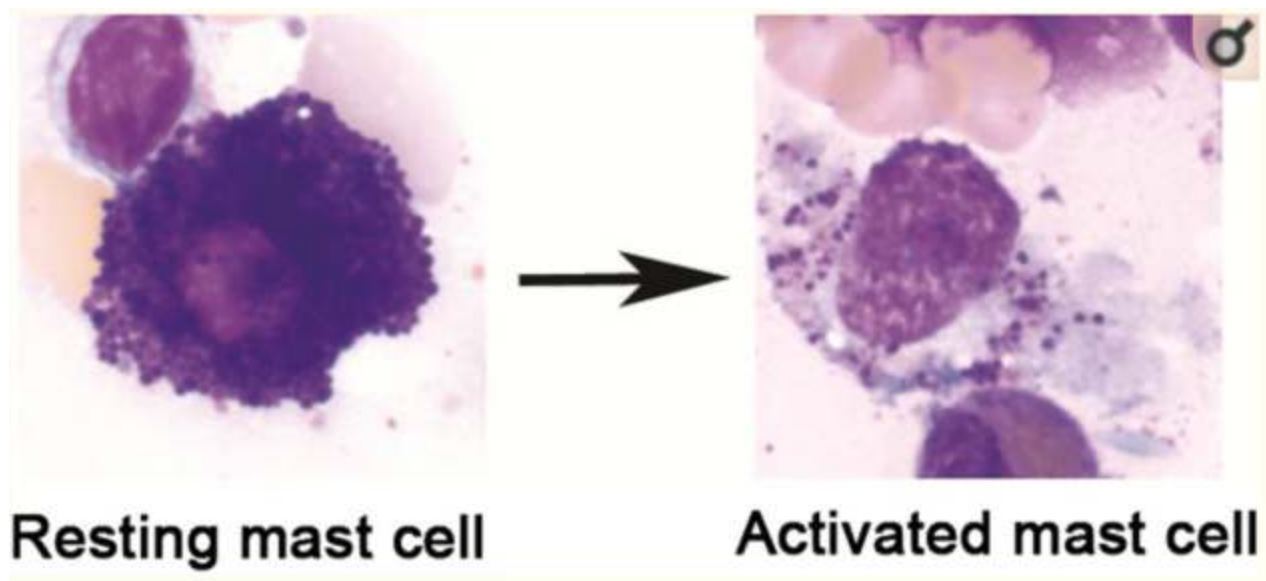
**TNF-alpha** is also found in mast cells. It is an inflammatory cytokine binding to receptors on the surface of endothelial (blood vessel) cells, making endothelial cells turn on adhesion molecules and recruit more immune cells...

**Second:** There is also a **later response** that happens hours after the initial degranulation.

Mast cells can turn on genes and make proteins such as IL-4, which stimulates Th2 cell production. Mast cells also produce chemokines such as CCL3, which signal monocytes and neutrophils to the area. GM-CSF, made in mast cells, targets bone marrow stem cells, telling them to differentiate into basophils and monocytes. Basically, this calls up reserve troops for the immune response to continue fighting off the pathogens.

**Prostaglandins and leukotrienes** are also synthesized by mast cells. These induce inflammation. Leukotrienes are 100 times more potent than histamine but have similar actions. Prostaglandins cause inflammation via vasodilation, vascular permeability, and more immune cells to become attracted to fight the infection. Prostaglandin also induces pain via binding to sensory neurons. Prostaglandins are synthesized from arachidonic acid using cyclooxygenase (COX), and you can inhibit prostaglandin response via aspirin or NSAIDs (e.g. ibuprofen).

Overall, mast cells have **50 – 200 granules in the cytoplasm** of the cell storing histamine, heparin, tryptase, cytokines, etc.[[ref](#)] The image below shows mast cell (stained purple) degranulation under a microscope.[[ref](#)]



[Image of a mast cell that has degranulated \(Creative Commons License\)](#)

### **Allergies: (Type I hypersensitivity reactions)**

In addition to reacting to antigens on a pathogen, such as a bacteria, the IgE can also be primed to link with antigens on proteins that are not pathogens – called **allergens**.

Common allergens include pollen, cats, dust mites, nuts, dairy, and fish.



The entire 'becoming allergic to something' process is quite involved. The common protein must be taken in by macrophages or dendritic cells to start the process, causing an antigen presentation on MHC II molecules. It tends to happen with inherited MHC-II types – certain HLA types. When these antigens are presented, they could run into a CD4 receptor that activates the CD4 T cells. It could prime the T-cell to become a TH2 helper T-cell if IL-4 is present. B-cells do something here also... if they also have the allergen protein that they have phagocytosed and presented then B-cell binds to the Th2 cell and creates IgE. The IgE binds to the mast cells.

If the allergen comes back, it binds to those IgE on mast cells and causes degranulation. What happens in the allergic response depends on where the mast cells become activated (gut, airway, skin, etc). For example, inhaled airborne allergens bind to IgE on the mast cells and trigger a response. Nose = allergic rhinitis (swelling, fluid, sneezing) Lungs – allergic asthma, fluid and mucus deep in the lungs, bronchial constriction, coughing.

### **Viruses and mast cells:**

While textbook information on mast cell activation usually mentions **parasites (worms), bacteria, and allergens, more** recent research shows that **viruses also activate mast cells**. A 2015 paper shows influenza A virus directly activates mast cells, causing the release of cytokines and contributing to the excessive inflammatory response in the lungs.[\[ref\]](#) Animal studies show that this pattern of mast cell activation and excessive response holds true for several strains of the flu. Additionally, mast cell inhibitors dramatically reduced lung lesions and mortality rates from the flu.[\[ref\]](#)

## **Other substances that activate mast cells:**

**IgE activation is just one way** a mast cell activates during its normal, pathogen-fighting function.

The following are known triggers of mast cell degranulation (in addition to IgG activation via pathogen or allergen):[\[ref\]](#)

- Acetylcholine
- Complement fragments ( $C3\alpha$ ,  $C4\alpha$ ,  $C5\alpha$ )
- Various drugs
- Peptides (including endorphins, leptin, PTH)
- Physical conditions (cold, heat, pressure, stress, vibration)

Additionally, mast cell activation can occur by IgG-antigen complexes, pathogen-associated molecular patterns (PAMPS), cell-cell contact, and hormones.[\[ref\]](#)

## Key points about mast cells:

- An essential part of the immune system, mast cells reside near all of the body's external surfaces (skin, intestine, lungs) as well as on the outside of blood vessels, in connective joint tissue, and near peripheral nerves.[\[ref\]](#)
- The mast cell precursors form from bone marrow stem cells and travel through the blood to different tissues, where they will mature and reside.[\[ref\]](#)
- Mast cells in different tissues act differently — secreting different chemicals when activated. For example, some release only tryptase and others only chymase (both along with histamine, IL-6, TNF-alpha, prostaglandins, etc.).[\[ref\]](#)
- Allergens and pathogens cross-link with IgE and activate mast cells. It causes an immediate release of almost all the granules (containing serotonin, histamine, chemokines, cytokines, enzymes, heparin, prostaglandins), which trigger itching, swelling, mucous, and anaphylaxis.[\[ref\]](#)
- A delayed response by mast cells comes from their formation of other mediators such as prostaglandin D2.
- Mast cells can also activate through receptors other than IgE-mediated and will only release certain, specific granules (e.g., just histamine).
- Mast cells can also become overly sensitized (more below) and degranulate due to substances produced within the body or physical conditions.

## When mast cells misbehave...

Homeostasis is a term applied to things being in balance in the body — not too much and not too little. That is also a key point here. We need mast cells for an immune response to fight bacteria when we get a cut on our finger. But overactive mast cells — either too many made or trigger too easily — can cause a cascade of different symptoms.

There are a variety of different consequences if mast cells don't behave normally. Some of the research reaches back decades, but a lot of the research is new. Definitions of diagnosis and understanding of the underlying nature of these diseases are still evolving. (In other words – forgive me if I didn't define something in a way more familiar to you.)

**Mast cell activation disorders**, which is an umbrella term covering several distinct diseases, include:

1. **Systemic mastocytosis** (too many mast cells)
2. **Mast Cell Leukemia**
3. **Mast Cell Activation Syndrome** (MCAS)

## 1) Systemic Mastocytosis:

Mastocytosis is a condition caused by a **proliferation of mast cells** due to too many being created and released in the bone marrow. These mast cells can then accumulate in various organs. For 80%-90% of people with systemic mastocytosis, a **mutation in the KIT gene** is the cause. The KIT mutations are not inherited, but instead, they arise spontaneously during a cell division (similar to cancer mutations). The KIT gene controls mast cell creation from stem cells in the bone marrow, and mutations in KIT cause excess mast cell proliferation.[\[ref\]](#)[\[ref\]](#)

A mastocytosis diagnosis is either systemic mastocytosis (affecting the whole body) or cutaneous mastocytosis, which shows up more in the skin.



While the KIT mutations in mastocytosis are not inherited from a parent, people with mastocytosis are more likely to have a first-degree relative with it. This leads researchers to assume that there is a heritable component to mastocytosis as well (e.g. other genes involved) — they just don't know what it is, yet.[\[ref\]](#)[\[ref\]](#)

Interestingly, about half of all kids with cutaneous mastocytosis tend to outgrow it and go into long-term remission. It is another reason to think that there is something else going on besides the KIT gene mutations.[\[ref\]](#)

Often, people with mastocytosis are treated with histamine receptor targeting drugs as well as other pharmaceutical interventions. It is considered to be a life-long condition for most adults.

In addition to KIT mutations, systemic mastocytosis also has links to mutations in the JAK2, PDGFR $\alpha$ , NRAS, RASGRP4, CBL, IL4, TET2, and IL13 genes.[\[ref\]](#)

There are specific markers used to distinguish and diagnose systemic mastocytosis, including [the World Health Organization](#) criteria.

## **2) Mast Cell Leukemia:**

Advanced mast cell disorders include a type of leukemia called mast cell leukemia. This rare condition is caused by the creation of a large number of atypical mast cells. This type of leukemia progresses rapidly...[\[ref\]](#)

## 3) Mast Cell Activation Syndrome

Mast Cell Activation Syndrome (MCAS) is **a systemic auto-inflammatory disease that can affect multiple organs**. There are a variety of clinical presentations and symptoms of this syndrome. For some people, it manifests as an almost constant allergic reaction state — like an allergy to almost everything. But for others, there are many non-allergic symptoms.

While more severe forms are not all that common, some research estimates that MCAS could “affect up to 17% of the population on a spectrum from very mild to debilitating symptoms.”[[ref](#)] Others include very mild symptoms such as allergic rhinitis in the mast cell activation spectrum, which includes up to 30% of the population.[[ref](#)]. Basically, it depends on how you define it.

In general, clinicians tend to diagnose mast cell activation syndrome in people with more severe symptoms, and patients often see multiple doctors in search of a diagnosis.

## Symptoms of Mast Cell Activation Syndrome:

Symptoms of mast cell activation syndrome can be broken down into the following categories:[[ref](#)]

- Dermatological symptoms: swelling, flushing, itching, hives, dermatographia (skin reaction when scratched)
- Gastrointestinal symptoms: abdominal pain, bloating, diarrhea, heartburn, nausea/vomiting
- Respiratory symptoms: hoarseness, sore throat, stridor, throat swelling, wheezing
- Neurological symptoms: headache, brain fog, peripheral neuropathy, tingling
- Musculoskeletal symptoms: bone or muscle pain, osteoporosis, degenerative disc disease
- Nose and eye symptoms: congestion, itching, and watery eyes
- Cardiovascular symptoms: chest pain, low blood pressure, altered heart rhythm
- Systemic symptoms: anaphylaxis, fatigue

People with mast cell activation syndrome will usually have **some, but not all**, of the above symptoms.

So what are the **most common symptoms of MCAS**? A survey of people with a mast cell activation syndrome diagnosis found that 94% had abdominal pain, and 89% had skin-related issues (dermatographism and flushing). Other common symptoms included headache, diarrhea, and memory or concentration difficulties.[[ref](#)]

Some researchers define mast cell activation syndrome as including symptoms from at least two different organ systems. For example, someone with cardiovascular symptoms wouldn't meet the criteria unless they also had gastrointestinal or dermatological symptoms.[\[ref\]](#)

One form of MCAS, now called '**idiopathic anaphylaxis**', involves sudden, often random-seeming, episodes of throat swelling, itching, wheezing, shortness of breath, stomach pain, nausea, vomiting, diarrhea, and a drop in blood pressure. In short, an anaphylaxis episode occurs without the presence of an allergen.[\[ref\]](#)

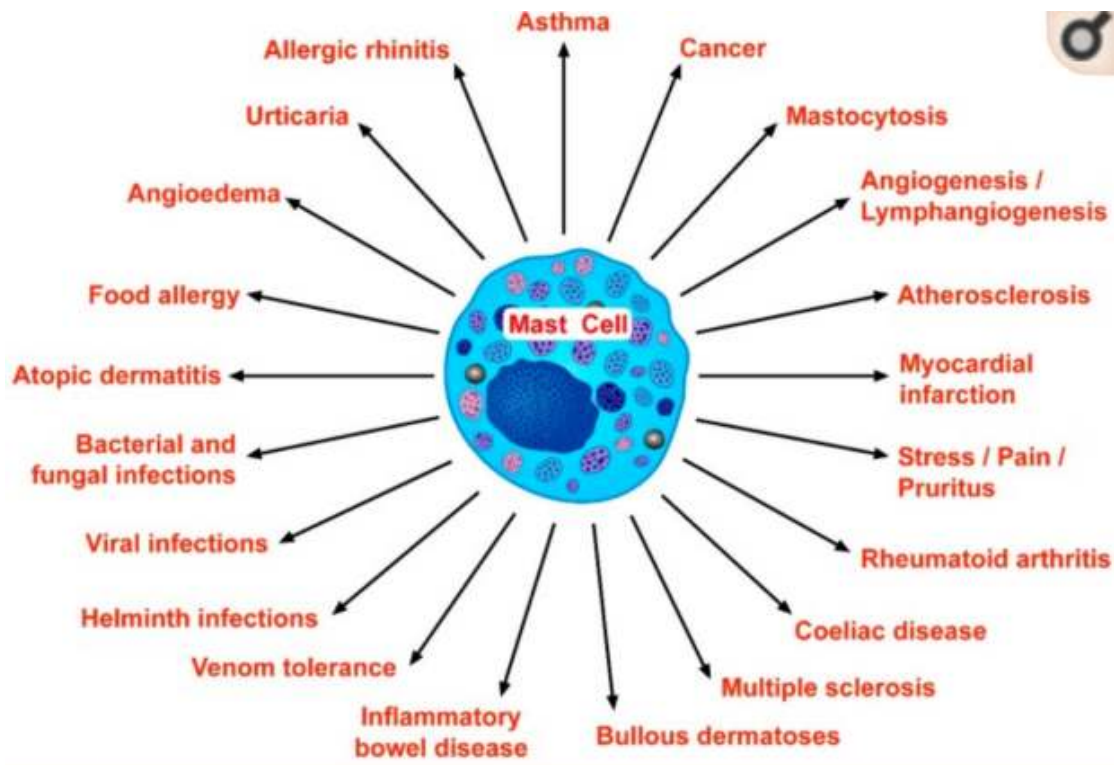
Another subtype of MCAS (at least according to some researchers) is **histamine intolerance**. Characterized by histamine-related symptoms, consuming foods high in histamine can make it worse. (Read more about [histamine intolerance and genes](#))

Many other conditions have mast cell activation as a component, including:

- idiopathic abdominal pain
- GERD (heartburn)
- chronic urticaria
- fibromyalgia
- atypical drug and insect bite reactions
- allergies
- chronic sinusitis
- pharyngitis and vocal tension
- dermatographism
- chronic headaches
- interstitial cystitis
- atrial fibrillation



Below is an image from a recent scientific review of mast cells covering many conditions involving mast cell activation. (Creative Commons license)[[ref](#)]



Finally, some researchers point out the growing evidence of mast cell involvement in several different **autoimmune diseases**, including MS, type 1 diabetes, and rheumatoid arthritis.[[ref](#)]

## Mast cell triggers and mediators:

There are a variety of **substances within the body** that researchers have found will trigger mast cells to release mediators without complete degranulation. These include: [\[ref\]](#)

- inflammatory cytokines (IL-1B, IL-33), which cause the release of IL-6, TNF, IL-8, and VEGF
- heavy metals (aluminum, cadmium, mercury)
- herbicides (atrazine, glyphosate)
- pathogens (Lyme disease, lipopolysaccharides from bacteria, certain viruses, and mold spores)

These triggers can cause a **two-phase reaction**:

- The mediators that mast cells can release immediately (within 1-5 minutes) include histamine, TNF, tryptase, RANKL, and serotonin. Mast cells can also synthesize and release prostaglandins D2 and leukotrienes quickly.
- Later (6 – 24 hours after stimulation), mast cells produce and secrete certain chemokines (TNF, CCL2, CCL8) and renin.[\[ref\]](#)

The different mediators released can lead to different symptoms of mast cell activation syndrome:

- **Histamine** leads to headaches, migraines, low blood pressure, itching, stomach acid release (and much more)
- **Tryptase** causes inflammation and fibrinogen lysis.
- **Prostaglandin E2** also produces inflammation and pain. It can manifest itself in a variety of ways. For example, animal studies show mast cells in the colon release prostaglandin E2, causing pain and hypersensitivity in IBS (irritable bowel syndrome). Colon biopsies from IBS-D patients also showed increased levels of prostaglandin E2. Using either a mast cell stabilizer or a medication to reduce prostaglandin E2 synthesis (e.g. a COX2 inhibitor) stopped the hypersensitivity in the animal model of IBS.[\[ref\]](#)

In the Lifehacks section, you'll find a further list of substances that also trigger mast cell degranulation.

### IL-6 and Mast Cells:

IL-6 plays an interesting role here. Interleukin-6 (IL-6) is a cytokine produced by several different immune system cells in response to infection and acute inflammation. IL-6 levels become elevated in people with systemic mastocytosis, chronic urticaria, and asthma. Constant IL-6 exposure can cause the body to form more reactive mast cells. One study concludes the IL-6 enhanced mast cells have "significantly enhanced FcεRI-mediated signaling, degranulation, and cytokine production".[\[ref\]](#)

## **Asthma and mast cell activation:**

Mast cells are abundant near the epithelial cells lining the lungs. Researchers theorize that asthma may be due to either inappropriate mast cell activation or that the mast cells are hyper-secretory.[\[ref\]](#)[\[ref\]](#)

One study sums up that mast cells release “preformed mediators including chymase, tryptase, and histamine and de novo synthesized mediators such as PGD<sub>2</sub>, LTC<sub>4</sub>, and LTE<sub>4</sub> in addition of cytokines mainly TGFβ<sub>1</sub>, TSLP, IL-33, IL-4, and IL-13 participate in the pathogenesis of asthma.”[\[ref\]](#)

## **Mast cells as a causative factor in osteoarthritis:**

Osteoarthritis, the most common form of arthritis, is caused by inflammation and degeneration of the joint tissue. Researchers and doctors have known that for years – inflammation, heat, pain, and the eventual remodeling of the joint (e.g. knobby toes and gnarled fingers).

Recently, researchers have found that excessive mast cell degranulation in the joints is the cause of osteoarthritis.[\[ref\]](#)

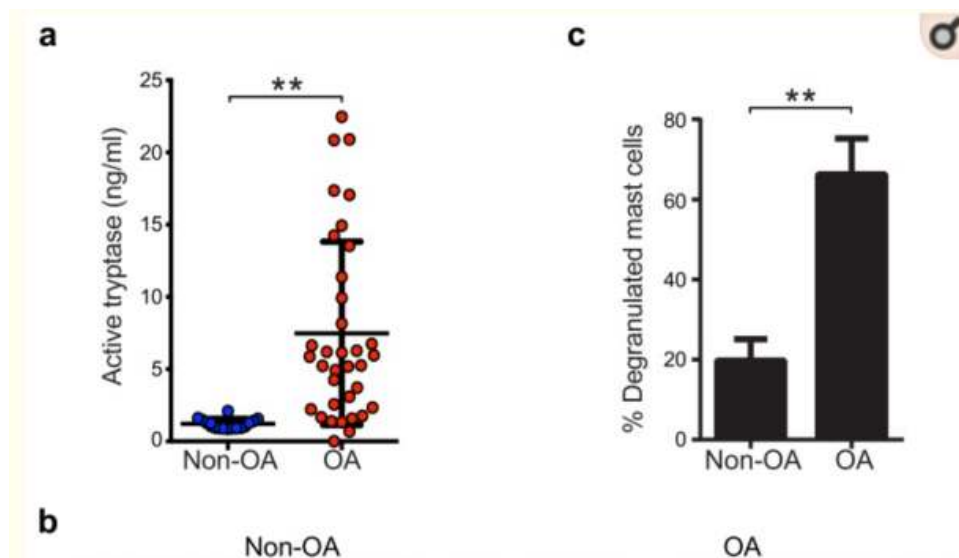
To prove this, researchers looked at both human joints and genetic models using mice. They found that if you reduce mast cells genetically in mice, they can't get osteoarthritis. Additionally, they were able to show that activation of mast cells in osteoarthritis is through IgE/FcεRI.



Going one step further, researchers showed that tryptase and the number of mast cells are both elevated in the joints of people with osteoarthritis. The activation of mast cells caused the destruction of neighboring chondrocytes and the breakdown of cartilage.

[[ref](#)]

The figure below is from a study on mast cells in osteoarthritis, showing both increased numbers of mast cells and an increase in tryptase. (Creative Commons License)[[ref](#)]



## Chronic urticaria (hives, itchiness):

Unsurprisingly, chronic urticaria is linked to mast cell activation and histamine release. Chronic urticaria is defined as having episodes of itchy wheals or hives on the skin, with the chronic part meaning it happens (intermittently) for six months or more.

Some people with chronic urticaria have autoantibodies against the FcεRI receptor or against IgE — but it doesn't seem to be an autoimmune condition for everyone.

Regardless of the initiating cause, mast cell degranulation is involved.[\[ref\]](#)

The first thing most clinicians recommend for chronic urticaria is non-sedating antihistamines that block the H1 receptor. It works for a portion of patients but not for everyone. Genetics plays a role here, and people who have genetically lower IgE levels are less likely to have chronic urticaria.[\[ref\]](#)

### **Mast cells, atrial fibrillation, and cardiac diseases:**

The research on mast cells in heart disease is fairly new – and interesting.

Researchers estimate that there are ~50,000 mast cells/g of human heart tissue. They lie just outside the epithelial cells that make up blood vessels and in the areas surrounding the nerves and myocytes. In heart failure and cardiomyopathy, the number of mast cells is greatly increased.[\[ref\]](#)

Atrial fibrillation (a-fib) is a heart arrhythmia that includes a rapid atrial activation and an irregular response in the ventricle. There are several very interesting studies explaining how mast cells are involved in causing a-fib. There is fibrosis in the atrium in hearts with a-fib, with an accumulation of extracellular matrix (ECM) proteins. This increase in ECM proteins – fibrosis – separates the individual bundles of muscle cells and disturbs the impulse propagation that causes the heart to beat regularly.[\[ref\]](#)

Animal studies from about a decade ago show a pressure overload in the heart (stressing out the heart) can cause mast cells to proliferate. When these mast cells infiltrate the atrium, it induces PDGF-a (platelet-derived growth factor), which causes fibrosis in the mouse heart, causing a-fib. In mice bred to be deficient in mast cells (kit mutation), the fibrosis and a-fib did not develop.[[ref](#)]

Mast cells are also implicated in the narrowing of the arteries due to atherosclerosis and play a role in stress-induced coronary artery disease. Oxidized LDL cholesterol can trigger mast cells.[[ref](#)][[ref](#)]

Another study on mast cells and oxidized LDL: “The results of this work indicate that the co-activation of macrophages and mast cells by oxLDL is an important mechanism for the endothelial dysfunction and atherogenesis. The observed synergistic effect suggests that both macrophages and mast cells play a significant role in the early stages of atherosclerosis. Allergic patients with a lipid-rich diet may be at high risk for cardiovascular events due to high concentrations of low-density lipoprotein and histamine in arterial vessel walls.”[[ref](#)][[ref](#)]

### **Interstitial cystitis as a mast cell disease:**

Interstitial cystitis, or painful bladder syndrome, is a disease that feels like a constant bladder infection. One cause (among several) of interstitial cystitis is overactive mast cells in the bladder. Allergens or toxins in the urine are thought to cause the bladder walls to become sensitized to increased mast cells.[[ref](#)][[ref](#)][[ref](#)]

## **Vulvodynia and mast cell activation:**

Vulvodynia is a chronic genital pain condition that includes increased numbers of mast cells. This condition is prevalent in about 8% of adult women, although it isn't talked about much.[\[ref\]](#)

Animal studies show certain preservatives often used in body washes and shampoos can cause "increased vaginal mast cells and eosinophils and had higher serum Immunoglobulin E". Specifically, researchers used methylisothiazolinone, found in hundreds of personal care products including vaginal wash products. The solution here was vaginal administration of THC (the active component of marijuana) to the mice... (how would you like that job :-).[\[ref\]](#)

## **Mast cells and rheumatoid arthritis:**

Rheumatoid arthritis is an autoimmune disease causing painful inflammation of the joints. The joints of people with rheumatoid arthritis contain high levels of mast cells and other immune cells such as T-cells and B-cells. Recent studies on rheumatoid arthritis show that it is more complex than initially thought of as an autoimmune response to certain antibodies. Mast cells are now thought to play a pathogenic role in the condition as well.[\[ref\]](#)

Researchers have found that the average prostaglandin D2 levels (an indicator of mast cell activation) are higher in people with rheumatoid arthritis than in healthy controls.  
[\[ref\]](#)



## **Mast cells may play a role in obesity:**

It has been known for a while that obesity is linked to increased systemic inflammation. Interestingly, fat cells (adipocytes) recently have been shown to contain mast cells. One of the peptides that trigger mast cells is leptin, which is produced at higher levels in people with more fat mass. These adipocyte mast cells then release pro-inflammatory cytokines, including TNF-alpha, and increase inflammation even more. Indeed, researchers found obese individuals to have higher levels of mast cell-derived tryptase. [\[ref\]](#)[\[ref\]](#)

Taking this one step further, some researchers link increased inflammation due to mast cell activation in adipose tissue as a cause of diabetes. Animal studies show mast cell stabilizing agents (cromolyn and ketotifen) can reduce both obesity and diabetes. In mice bred to be deficient in mast cells, even an obesity-inducing diet doesn't cause the expected weight gain.[\[ref\]](#)[\[ref\]](#) Other research, though, claims mast cells have nothing to do with obesity. It depends on which genes are varied in the research animals and perhaps what makes up the high-fat diet.[\[ref\]](#)

Are mast cells at the root of everyone's weight problem? I don't think that is clear from the research — and there are a lot of different components of appetite regulation, fat storage, and base metabolic rate that come into play with obesity. Instead, mast cells may be what drives excess inflammation — in some people who are obese. One dietary difference in the activation of mast cells in obesity (in animal studies) is cholesterol levels. Again, this is an animal study, so it may not hold true for humans. But in animals fed a high-fat diet, mast cell inhibitors stopped the inflammation and histamine release and stopped the weight gain. It was true, though, only in diets that contained cholesterol.[\[ref\]](#)

### **Role of mast cells in rosacea:**

Rosacea is an inflammatory skin condition that plagues many people. Animal studies show mast cells are involved in inflammation, and a deficiency of mast cells caused the animals not to have rosacea. There are several mediators here that can cause mast cells to degranulate in skin tissue with rosacea. These include host defense peptides, such as LL-37, as well as substance P (pain neurotransmitter), VIP (vasoactive intestinal peptide), and serotonin. When activated, the mast cells in the skin release mediators (histamines, tryptase, TNF-alpha, CXCL9, etc) that cause inflammation, flushing, itching, or burning.[\[ref\]](#)

## **Dermatographism and mast cell activation syndrome:**

In a survey of mast cell activation syndrome, dermatographism was found in 89% of the patients.[\[ref\]](#) Dermatographism is when you get welts or raised red lines when you scratch your skin lightly. It can also happen due to pressure or rubbing. It is also called dermographia, dermatographic urticaria, or skin writing, and tends to get lumped into atopic dermatitis diagnosis.[\[ref\]](#)

Cold urticaria (hives or welts due to cold) or cold-dependent dermatographism, another mast cell-related condition, happens when the skin is lightly scratched after being chilled.[\[ref\]](#)

## **Peripheral neuropathy and mast cell activation:**

Neuropathy causes numbness, pain, pins and needles, and weakness, usually in the hands and feet. It is usually caused by damage to the peripheral nerves due to diabetes, infections, injuries, or toxins.

Mast cells are found in the area around the terminal ends of peripheral nerves. Upon degranulation, they release histamine, stimulating the nerve to release substance P and glutamate from the nerve terminals. It can actually start a cycle where the nerve releases substances that activate the mast cells, releasing mediators that activate the nerve. Researchers theorize this may be one of the causes of various chronic pain syndromes, including neuropathy.[\[ref\]](#)[\[ref\]](#)

## **Celiac disease onset and progression:**

Researchers recently found that the severity of intestinal damage in celiac disease relates to the number of mast cells in the area. Additionally, mast cells directly respond to gliadin fragments (part of the gluten protein) and release proinflammatory mediators.[\[ref\]](#)

## **Overlapping conditions with mast cell activation syndrome:**

### **Ehlers-Danlos and Mast Cell Activation:**

As mentioned above, mature mast cells are found in tissues and congregate in the connective tissue around lymphatic vessels, blood vessels, nerves, and skin. One syndrome that can go hand-in-hand with mast cell activation syndrome is Ehlers-Danlos, a tissue connectivity disorder. People who have Ehler's Danlos can have increased joint hypermobility, skin hyper-elasticity, vascular fragility, varicose veins, orthostatic intolerance, asthma, and osteoporosis. Researchers have noted an overlap that often occurs between people with Ehlers-Danlos and mast cell activation syndrome.[\[ref\]](#)

*Related article:* [Check your 23andMe data for Ehlers-Danlos Syndrome genes](#)

## **POTS – Postural orthostatic tachycardia syndrome:**

There is an overlap in some patients between MCAS and postural orthostatic tachycardia syndrome (POTS), a common type of dysautonomia. Pretty much all the research on the topic, though, says there are a lot of unanswered questions here and more research is needed.[\[ref\]](#)[\[ref\]](#)

*Related article:* [POTS syndrome genes](#)

## **Restless Leg Syndrome:**

A recent study found people with mast cell activation syndrome were about 3 to 4 times more likely than normal to have restless leg syndrome also.[\[ref\]](#)

## **Markers and testing for mast cell activation syndrome:**

The symptoms associated with mast cell activation vary widely. How do you know if this is the root of your problems? How do doctors make the diagnosis?

It turns out that there are some markers that can be tested — but these tests all have shortcomings. Specific measures need to be taken with storage and blood collection to prevent false negatives. Time of day and proximity to a triggering event are also important.[\[ref\]](#)

## **Tryptase as a biomarker of mast cell activation syndrome:**

Serum tryptase, an often tested biomarker, can determine if someone is likely to have mast cell activation syndrome. Elevated tryptase, along with symptoms of mast cell activation syndrome, can be used by some doctors to make an MCAS diagnosis.

Considered the most specific marker, tryptase needs to be measured within 4 hours of an episode and then compared with a baseline measurement.[\[ref\]](#)

But... it also turns out that a portion of the population has genetically elevated tryptase levels. A genetic condition called hereditary alpha-tryptasemia occurs in about 4-6% of the population. It is thought to be due to carrying extra copies of the TPSAB1 gene.[\[ref\]](#)

## **Histamine release from mast cells:**

One of the mediators released from mast cells is histamine, which most people associate with allergic reactions. Histamine is what you think of for sinus drainage, hives, watery eyes, and stomach issues.

A recent publication notes measuring histamine levels to be a simple, non-invasive test for people suspected of having mast cell activation syndrome. The increase in histamine levels can occur independently of tryptase in MCAS.[\[ref\]](#)

You can order plasma histamine or n-methylhistamine (urine) tests for yourself via [Ultralab Tests](#) — but they are relatively expensive. However, this may be a test that your doctor could easily order for you if it is cheaper to go through your health insurance.

## Prostaglandin and mast cells:

Prostaglandin, another mediator, can be elevated in people with MCAS, again independent of tryptase levels. And again, you can order a test through [Uta Lab tests](#), but it is expensive. Going through your doctor may be a better bet on this.

## Mast Cell Genotype Report:

### Genetic variants related to mastocytosis:

**KIT gene:** mutations that cause systemic mastocytosis — included here just for informational purposes. I don't think 23andMe data can/should be used for determining somatic KIT mutations. Instead, you would need a biopsy done through your physician to determine whether the KIT mutation is found in specific cell types in your body.

Check your genetic data for **rs121913507** (23andMe i5007903 v4; AncestryDNA):

- A/A: typical
- A/T: KIT D816V mutation, systemic mastocytosis
- T/T: KIT D816V mutation, systemic mastocytosis[[ref](#)]

**IL-13 gene:** encodes an inflammatory cytokine

Check your genetic data for **rs1800925** (23andMe v4, v5; AncestryDNA):

- C/C: typical
- C/T: increased risk of systemic mastocytosis, rhinitis, and asthma
- T/T: increased inflammatory response,[[ref](#)] increased risk of systemic mastocytosis[[ref](#)] increased rhinitis and asthma[[ref](#)]

**IL4R gene:** codes for the interleukin-4 receptor.

Check your genetic data for **rs1801275** (23andMe v4; AncestryDNA):

- G/G: typical
- A/G: in people with KIT mutations and systemic mastocytosis, this variant lowers the disease markers and gives a better prognosis[\[ref\]](#)
- A/A: in people with KIT mutations and systemic mastocytosis, this variant lowers the disease markers and gives a better prognosis[\[ref\]](#)

## **Genetic Variants linked with other mast cell-associated issues:**

Let me be clear: I'm not saying that any of these variants specifically cause mast cell activation syndrome. There are no genetic studies – as of right now – that say that a certain SNP causes someone to have mast cell activation syndrome. Instead, I suspect that there are a lot of genetic variants that interact with various environmental factors to cause MCAS. But with a newly defined syndrome, there is no hard data on this.

Instead, the variants below involve various conditions linked to mast cell degranulation, such as higher IgE levels, chronic sinus issues, and chronic urticaria (hives).



**FCER1A gene** codes for the mast cell receptor (FceRI $\alpha$ ) to which IgE binds. Higher IgE levels could lead to more mast cell degranulation.

Check your genetic data for **rs2298805** (23andMe v5 only)

- G/G: typical
- A/G: half the risk of chronic urticaria (itchiness); lower serum IgE levels; antihistamines likely to be more effective for chronic urticaria
- A/A: half the risk of chronic urticaria (itchiness); lower serum IgE levels; antihistamines likely to be more effective for chronic urticaria[[ref](#)]

Check your genetic data for **rs2251746** (23andMe v4, v5; AncestryDNA)

- C/C: lower IgE levels[[ref](#)]
- C/T: lower IgE levels
- T/T: typical

Check your genetic data for **rs2427827** (23andMe v4, v5; AncestryDNA)

- C/C: typical
- C/T: higher serum IgE levels; increased risk of chronic rhinosinusitis (sinus issues and nasal drainage), atopic dermatitis, and allergic-type reactions in general
- T/T: higher serum IgE levels; increased risk of chronic rhinosinusitis (sinus issues and nasal drainage), atopic dermatitis, and allergic-type reactions in general[[ref](#)]  
[[ref](#)][[ref](#)]

**CMA1 gene:** codes for mast cell chymase (one of the mediators released by mast cells)

Check your genetic data for **rs1800875** (23andme v4; AncestryDNA)

- C/C: typical
- C/T: lower risk of atrial fibrillation[\[ref\]](#) lower IgE levels[\[ref\]](#)
- T/T: lower risk of atrial fibrillation[\[ref\]](#) lower IgE levels[\[ref\]](#)

**PTPN22 gene:** codes for the protein tyrosine phosphatase nonreceptor type 22, which is associated with various autoimmune diseases. One of its functions is in synthesizing AEA, which is one of the body's endocannabinoids. Another function is to inactivate the T-cell response. Genetic variants that decrease or eliminate PTPN22 have links to constantly activated T-cells, which cause over secretion of pro-inflammatory cytokines and inflammation.

Check your genetic data for **rs2476601** R620W (23andMe v4; AncestryDNA):

- G/G: typical
- A/G: decreased PTPN22, increased risk of psoriasis, arthritis, rheumatoid arthritis, increased T-cell proliferation due to environmental triggers.[\[ref\]](#) type 1 diabetes, lupus[\[ref\]](#) increased risk of chronic urticaria[\[ref\]](#)[\[ref\]](#)
- A/A: greatly decreased PTPN22, increased risk of psoriasis, arthritis, rheumatoid arthritis, increased T-cell proliferation due to environmental triggers.[\[ref\]](#) type 1 diabetes, lupus[\[ref\]](#) increased risk of chronic urticaria[\[ref\]](#)[\[ref\]](#)

**IL-33 gene:** codes for interleukin-33, which causes mast cells to produce cytokines, such as Il-6. Genetic variants have links to asthma, increased IgE, and airway hyperresponsiveness.

Check your genetic data for **rs1342326** (23andMe v4, v5; AncestryDNA):

- A/A: increased risk of asthma[\[ref\]](#) increased risk of hay fever[\[ref\]](#)
- A/C: increased risk of asthma, increased risk of Behcet's disease[\[ref\]](#)
- C/C: typical

Check your genetic data for **rs3939286** (23andMe v4; AncestryDNA):

- T/T: increased risk of asthma[\[ref\]](#)[\[ref\]](#)
- C/T: increased risk of asthma
- C/C: typical

Check your genetic data for **rs928413** (23andMe v4, v5; AncestryDNA):

- G/G: increased risk of hay fever[\[ref\]](#) increased risk of atopic asthma[\[ref\]](#)
- A/G: increased risk of hay fever[\[ref\]](#) increased risk of atopic asthma[\[ref\]](#)
- A/A: typical

**ALDH2 gene:** codes for aldehyde dehydrogenase, which is the enzyme that breaks down aldehydes. Alcohol metabolizes into aldehydes, and the enzyme clears it out. Genetic variants here can cause a flushing reaction to alcohol. Animal studies show that decreased ALDH2 can cause increased KIT activity and increased mast cell activation via kit-mediated responses.[\[ref\]](#)

Check your genetic data for **rs671** (23andMe v4, v5; AncestryDNA):

- A/A: Alcohol flush reaction[\[ref\]](#), may cause slightly increased mast cell KIT activation (mouse study)[\[ref\]](#)
- A/G: Alcohol flush reaction
- G/G: typical acetaldehyde metabolism

## **Genetic variants related to prostaglandin synthesis from mast cells:**

**PTGS2 gene:** Prostaglandin-Endoperoxide Synthase 2 – also known as COX-2 enzyme that converts arachidonic acid into prostaglandin

Check your genetic data for **rs4140564** (23andMe v4, v5; AncestryDNA):

- A/A: typical
- A/G: increased risk of knee osteoarthritis[\[ref\]](#)
- G/G: increased risk of knee osteoarthritis[\[ref\]](#)

## Genetic variants linked with histamine intolerance:

The body breaks down histamine from foods via the diamine oxidase enzyme. AOC1 gene codes for the enzyme. People with lower diamine oxidase are more likely to notice effects from high histamine foods. The body breaks down histamine created within the body (such as from mast cells) using the HMNT enzyme.

*Related article:* Find out more about [histamine intolerance](#).

## AOC1 genetic variants (diamine oxidase):

Check your genetic data for **rs10156191** (23andMe v4; AncestryDNA):

- C/C: typical
- C/T: reduced production of DAO, increased risk of migraines due to histamine[[ref](#)]
- T/T: reduced production of DAO[[ref](#)][[ref](#)], increased risk of migraines due to histamine[[ref](#)]

Check your genetic data for **rs2052129** (23andMe v5 only):

- G/G: typical
- G/T: reduced production of DAO, increased risk of migraines due to histamine[[ref](#)]
- T/T: reduced production of DAO[[ref](#)], increased risk of migraines due to histamine[[ref](#)]

Check your genetic data for **rs1049742** (23andMe v4 only):

- C/C: typical
- C/T: reduced production of DAO
- T/T: reduced production of DAO[[ref](#)]

Check your genetic data for **rs1049793** (23andMe v4; AncestryDNA):

- C/C: typical
- C/G: reduced production of DAO
- G/G: reduced production of DAO[[ref](#)]

## **HNMT genetic variants:**

Histamine n-methyltransferase (HNMT) is the enzyme that regulates histamine in the body via converting it from histamine into N-methylhistamine, which can then be eliminated from the body.

Check your genetic data for **rs1050891** (23andMe v4, v5):

- G/G: typical
- A/G: reduced breakdown of histamine compared to G/G
- A/A: reduced breakdown of histamine compared to G/G[[ref](#)]

Check your genetic data for **rs11558538** C314T (23andMe results for i3000469, v4; AncestryDNA):

- T/T: reduced HNMT activity[[ref](#)][[ref](#)]
- C/T: reduced breakdown of histamine compared to C/C
- C/C: typical[[ref](#)]

## Lifehacks:

Below are evidence-based ways of preventing mast cells from degranulating, either by avoiding triggers or through substances that block various aspects of mast cell degranulation. If you are under a doctor's care or taking any medications regularly, be sure to check with your doctor before making any changes.

### Avoid substances that cause mast cell degranulation:

The following have been shown in studies to cause mast cells to degranulate. The majority of the studies are in cell cultures or animals, so YMMV. You may want to experiment with each one to see if they cause mast cell-related symptoms for you.

- Anything you are allergic to... traditional allergy testing can help a lot here.
- "Calcium triggers the secretion of histamine from mast cells after previous **exposure to sodium fluoride**."[\[ref\]](#) *Sodium fluoride is added to drinking water in most US municipalities.*
- **PFOA's** (Perfluorooctanoic acid) have been found to release histamine and cause mast cell degranulation. "... PFOA exacerbated allergic symptoms via hypothermia, and an increase of serum histamine, TNF- $\alpha$ , IgE, and IgG1 in the ovalbumin-induced systemic anaphylaxis. The present data indicate PFOA aggravated Fc $\epsilon$ RI-mediated mast cell degranulation and allergic symptoms."[\[ref\]](#) PFOA's are found in Teflon, stain-resistant carpeting, microwave popcorn bags, and other food wrappers, etc.
- Off-gassing from carpeting may cause mast cell release in cases of sick building syndrome[\[ref\]](#) (Note that this may overlap with PFOAs since they used to be used on stain-resistant carpets.
- **Sodium benzoate**, a common preservative, causes histamine release in people with allergies and asthma.[\[ref\]](#)

- Methylisothiazolinone, a really common preservative used in cosmetics, shampoo, and personal care products, has been shown to increase mast cells and IgE (animal and human allergy studies).[\[ref\]](#)[\[ref\]](#)[\[ref\]](#)
- **Glyphosate** (the active ingredient in RoundUp) has been shown to cause mast cell degranulation in the airways.[\[ref\]](#) In rats exposed to low dose RoundUp, the adipose tissue and liver cells had increased inflammatory markers, including prostaglandin D2 synthesis from mast cells.[\[ref\]](#)
- Endosulfan, a pesticide and wood preservative, causes mast cell release.[\[ref\]](#)
- **BPA** exposure in utero increases mast cells in adults (animal study).[\[ref\]](#) Human cell studies show that low levels of BPA increase histamine and leukotriene release from mast cells.[\[ref\]](#) (Read more about [BPA and genes](#))
- Mercury and silver in dental amalgam fillings have been shown to cause histamine release from mast cells.[\[ref\]](#)

While not a 'substance' per se, **psychological stress** causes mast cell degranulation.  
[\[ref\]](#)[\[ref\]](#)[\[ref\]](#)

### Diet:

**Allergy elimination diets** and **low-histamine diets** have been shown in studies to be helpful to some people with chronic itching (one symptom of mast cell activation syndrome). Researchers recommend a 3-week trial of any dietary intervention and only trying one intervention at a time.[\[ref\]](#)

Related article: [Histamine intolerance and a low histamine diet](#)



## Exercise:

In general, exercise is good for you. Lots of research shows that for the majority of people, exercise is a good thing. But... **exercise causes both histamine and tryptase levels to rise**. Research shows this is both due to de novo formation and mast cell degranulation. This release of histamine and tryptase increases blood flow to the skeletal muscles during exercise.[\[ref\]](#)

Hypoxia has also been shown to induce mast cell degranulation.[\[ref\]](#)

This is a normal response for most people, and the body can handle a certain increase in histamine and tryptase. Still, some people with mast cell activation syndrome may find that exercise is a definite trigger for a mast cell event.

This is another one of those 'experiment and track it' situations: Keep track of your workouts and note any mast cell-related responses over the following 24 hours. You should dial in the right amount of exercise that causes you the least amount of mast cell degranulation.

## Research on supplements that modify mast cell release:

The following supplements have research showing their effect on mast cell degranulation:

- **Cordyceps** extract has been shown in mouse models to prevent mast cell degranulation in the intestines.[\[ref\]](#)
- **Luteolin** decreases mast cell mediator release.[\[ref\]](#)
- **Ginkgoneolic acid**, a component of Ginkgo Biloba, inhibits mast cell degranulation.[\[ref\]](#)
- **Resveratrol** has been shown to inhibit prostaglandin formation by mast cells, but TNF-alpha production actually increased with resveratrol at low concentrations.[\[ref\]](#) Thus, resveratrol may be a supplement to try at varying dosages, but keep an eye out for any symptoms from increased TNF.
- **Euphorbia hirta**, a herbal Ayurvedic remedy for asthma, has been shown in animal studies to inhibit mast cell degranulation.[\[ref\]](#)
- **Quercetin** has been shown in animal studies to prevent the release of histamine from mast cells.[\[ref\]](#) (Read more about [quercetin](#).)
- **Naringenin**, a citrus flavonoid, reduces the proliferation of mast cells.[\[ref\]](#)[\[ref\]](#)
- **Chicoric acid**, found in echinacea and chicory, has been shown to inhibit mast cell activation and decrease TNF-alpha, IL-6, and histamine release.[\[ref\]](#)
- Extracts of vigna angularis (**Adzuki**, or red mung beans) have been shown to inhibit mast cell degranulation.[\[ref\]](#)

### PPARG agonist for blocking the formation of mast cells:

PPAR $\gamma$  agonists have been shown in cell studies to decrease the formation of mast cells from bone marrow stem cells.[\[ref\]](#) Interestingly, PPAR $\gamma$  agonists are commonly used as diabetes drugs (which ties in with the theory referenced above on diabetes, obesity, and mast cells).

## **Cannabinoids and endocannabinoids:**

Mast cells in the skin have been shown to have both CB1 (cannabinoid 1) and CB2 receptors. These are the receptors that cannabis binds to — as well as being activated by the cannabinoids made in our bodies (endocannabinoids). Interestingly, not all mast cells seem to have cannabinoid receptors, so keep in mind that the effects of both endogenous and exogenous cannabinoids may be limited to specific tissues.[\[ref\]](#)

CBD has been tested in mouse studies and shown **not** to inhibit mast cell degranulation in the heart.[\[ref\]](#) Other studies show that CBD triggers activation in some mast cells.[\[ref\]](#)

Palmitoylethanolamide (PEA), an endogenously produced cannabinoid, binds to the CB2 receptors. Mast cells in the skin have cannabinoid receptors, and PEA seems to control or reduce mast cell degranulation.[\[ref\]](#) Mast cells in the epithelial cells are also modulated by PEA, and less intestinal damage is accumulated in animals given PEA along with radiation injuries.[\[ref\]](#) You can buy PEA as a supplement.

Anandamide (AEA) is another endocannabinoid that binds to the CB1 receptors on mast cells. It has been shown to suppress mast cell proliferation and inhibit the release of inflammatory mediators.[\[ref\]](#)

## **Rapamycin:**

Rapamycin decreases mast cell mediator release.[\[ref\]](#)

## Aspirin and NSAIDs:

Within mast cells, prostaglandin D (a pro-inflammatory cytokine) is synthesized using COX1. The synthesis of prostaglandin D2 by mast cells can be controlled with NSAIDs or aspirin, which are COX1 inhibitors.[\[ref\]](#)[\[ref\]](#)

But... Aspirin can trigger mast cell degranulation for people who are hypersensitive to it — so proceed with caution if you don't know how you react to aspirin or other NSAIDs.  
[\[ref\]](#)

## Pharmaceutical options for MCAS:

Your doctor should help you out if you decide to go the route of traditional pharmaceutical drugs. There are a couple of ways of approaching MCAS:[\[ref\]](#)

- stopping the mast cells from degranulating (e.g. sodium cromolyn, ketotifen)
- managing symptoms with histamine receptor blockers (e.g. Benadryl, Zyrtec, Tagamet)
- inhibiting the mast cells from making the mediators (e.g. aspirin or zileuton)
- inhibiting IgE formation (Xolair)

## Conclusion:

Mast cells touch on a lot of organ systems and pathologies in the body. The more I learn, the more amazed I am at the complex interaction between mast cells, immune responses, and systemic diseases.

Wrapping up this article, I wanted everyone to know that this is just the tip of the iceberg when it comes to information and studies about mast cells and MCAS. Topics not covered include thyroid disorders, multiple sclerosis, dementia, mast cells in cancer, Crohn's, ALS, endometriosis, Hidradenitis suppurativa, and osteoporosis. (Yes – this is my list of things to come back and write more about later!)

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