VIRANT DIAGNOSTICS

CLIA Certified and CAP Accredited Laboratory

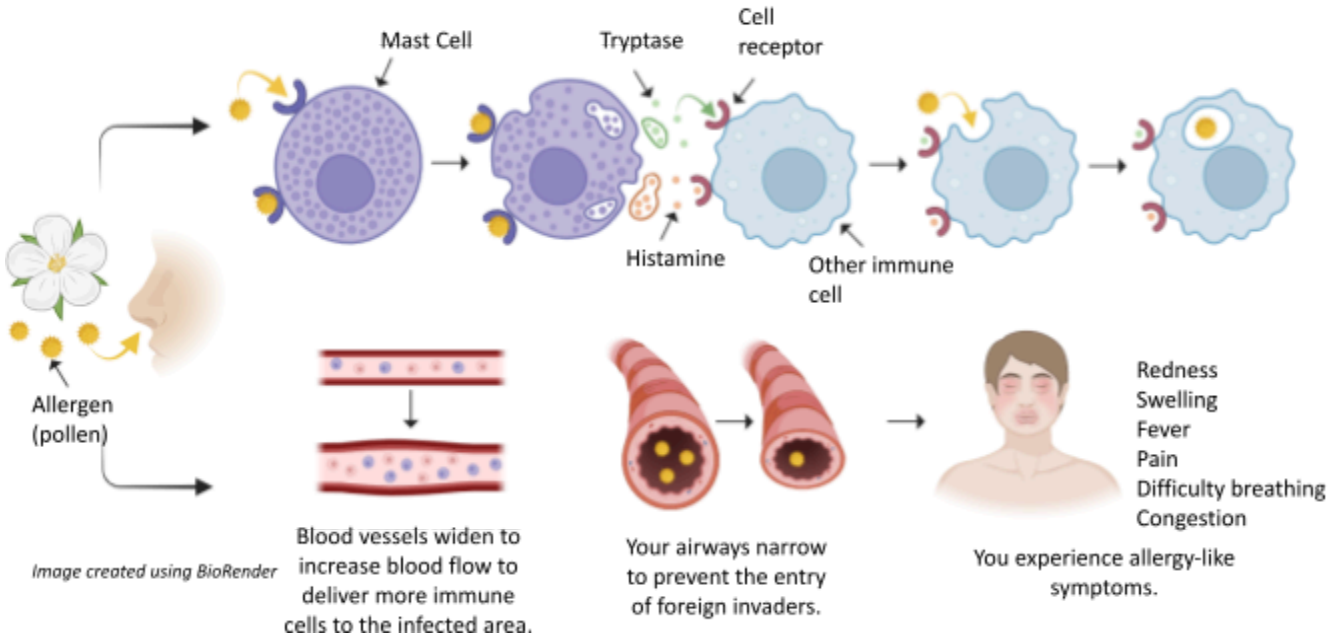
MAST CELL DISORDERS

For Patients

Your Immune System and the Inflammatory Response

Your **immune system** protects your body from infection with the help of various, specialized **immune cells**. Immune cells recognize when a foreign invader, such as an allergen or virus, enters your body. Then, they release chemicals, called **mediators**, that bind to **receptors** on other immune cells to trigger them to attack the foreign invader. This is one way your immune system protects the other cells in your body and keeps you healthy.

You may experience an **inflammatory response** when your immune cells are attacking a foreign invader. Even though your immune system is working to keep you healthy, you may experience some uncomfortable symptoms. Your blood flow may increase to deliver more immune cells to the site of infection, causing redness and swelling. You may feel hot and feverish as your body temperature increases to kill off the foreign invader. Your airways may tighten to prevent the foreign invader from entering your lungs, causing wheezing and shortness of breath. All of these symptoms, and other allergy-like symptoms, are the symptoms of an inflammatory response.



What are mast cell disorders (MCDs)?

Mast cells are a special type of immune cell. They are located throughout your body in areas that interact with the outside world, such as in your skin, lungs, and stomach. Mast cells recognize foreign invaders and release mediators; two important mast cell mediators are **histamine** and **tryptase**.

Mast cell disorders (MCDs) occur when the body produces too many mast cells and/or your mast cells are overreacting. This leads to an increase in the release of mast cell mediators. Increased levels of mast cell mediators cause the uncomfortable symptoms of an inflammatory response. So, patients with MCDs often experience recurring, severe allergy-like symptoms and may even experience anaphylaxis. MCDs include hereditary alpha-tryptasemia (HαT), systemic mastocytosis (SM), cutaneous mastocytosis (CM), and mast cell activation syndrome (MCAS).

What is hereditary alpha-tryptasemia (HαT)?

Virant Diagnostics, Inc.
11002 Veirs Mill Road, Suite 404, Wheaton, MD 20902
Website: virantdx.com Email: info@virantdx.com
Phone: 877-888-2973 Fax: 888-713-3456

Hereditary alpha-tryptasemia (HαT) is a genetic condition with additional copies of a gene called **TPSAB1**. The *TPSAB1* gene produces the mast cell mediator tryptase. Additional copies of the *TPSAB1* gene lead to elevated tryptase levels, causing inflammatory responses and HαT symptoms including:

- Anaphylaxis
- Skin flushing, itching, hives, swelling
- Palpitations, changes in blood pressure, dizziness, fainting
- Abdominal pain, bloating, diarrhea, nausea, vomiting
- Connective tissue abnormalities (e.g., joint hypermobility, retained primary teeth)

What causes HαT?

HαT occurs in approximately 5% of the general population. Normally, you only carry two copies of a gene, known as **alleles**. You inherit one allele from each parent. But in some cases, such as in HαT, a gene may duplicate and have 3 or more alleles. Then, increased copies of the gene lead to increased production of its protein. The *TPSAB1* gene encodes 2 different alleles, **α-tryptase** and β-tryptase. An increase in α-tryptase copies leads to increased production of tryptase.

How is HαT diagnosed?

HαT can be diagnosed with the **Alpha-tryptase Copy Number Variation** genetic test offered by Virant Diagnostics. This test determines the copy number of the *TPSAB1* gene. Your healthcare provider will collect a blood sample and send it to Virant Diagnostics. The genetics laboratory will perform the genetic test and analyze the results which will be reviewed by a certified geneticist before they are reported back to your healthcare provider. Your healthcare provider may also order a serum tryptase test to evaluate the level of tryptase in your blood before ordering the genetic test. Your healthcare provider will use the results of these tests to confirm or rule out a diagnosis of HαT.

What do my Alpha-tryptase Copy Number Variation test results mean?

The Alpha-tryptase Copy Number Variation test reports the number of α-tryptase and β-tryptase copies on the *TPSAB1* gene. Your result may be:

- Abnormal: Additional copies of the *TPSAB1* gene were detected. You have the HαT trait. The number of α-tryptase copies can be used to predict HαT disease severity (increased copies of α-tryptase are predictive of higher blood tryptase levels (i.e., a patient with 4 α-tryptase copies would have greater disease severity than a patient with 3 α-tryptase copies). Even if you carry the trait for HαT, you may not experience symptoms. However, you are still capable of passing down the trait and having a symptomatic child.
- Normal: Additional copies of the *TPSAB1* gene were not detected. You do not have the HαT trait.

What is systemic mastocytosis (SM)?

Systemic mastocytosis (SM) is a condition with too many mast cells in multiple parts of the body, other than just the skin. It is a rare disease that affects approximately 0.01% of the population. Symptoms of SM include:

- Anaphylaxis
- Skin flushing, itching, hives, swelling
- Wheezing, shortness of breath
- Sinus congestion, pressure
- Palpitations, changes in blood pressure, dizziness, fainting
- Abdominal pain, bloating, diarrhea, nausea, vomiting
- Anemia, bleeding disorders
- Uterine cramping, bleeding
- Bone/muscle pain, osteopenia, osteoporosis
- Enlarged liver, spleen, lymph nodes
- Headache, brain fog, short memory span

- Depression, anxiety, mood changes, problem concentrating

Certain triggers activate the extra mast cells, producing extra mediators and causing SM symptoms. Common triggers are:

- Changes in temperature (extreme heat/cold)
- Strong smells
- Vibration
- EMF (electromagnetic frequency)
- Heavy metals
- Sunlight
- Foods and beverages, particularly spicy foods and alcohol
- Social/emotional stress
- Exercise, fatigue, or other physical stress
- Insect stings
- Skin irritation/friction (e.g., massage)
- Certain medications (e.g., antibiotics, opioids, NSAIDs, neuromuscular junction blocking agents, local anesthetics, aspirin)
- Pathogens (e.g., mold, bacteria, viruses, parasites, and other foreign pathogens

What causes SM?

The most common cause of SM (~95% of cases) is a mutation in a gene called ***KIT*** (this mutation can not be inherited). The *KIT* gene regulates mast cell growth and development. A specific mutation in the *KIT* gene, known as ***KIT* D816V**, leads to increased numbers of mast cells. The extra mast cell cells produce extra mediators, such as histamine and tryptase, causing inflammatory responses and SM symptoms.

How is SM diagnosed?

Your healthcare provider will use a set of criteria to confirm or rule out a diagnosis of SM. Testing may include:

- Biopsy: examine the mast cells in your skin/bone
- Serum tryptase levels: determine the level of tryptase in your blood
- *KIT* D816V mutation testing: detect the *KIT* D816V mutation

The **High-Sensitivity *KIT* D816V Mutation Hotspot** test offered by Virant Diagnostics is the most highly sensitive test available for the detection of the *KIT* D816V mutation. High test sensitivity helps diagnose SM early and prevent the negative outcomes of a delayed diagnosis. Your healthcare provider will collect a blood sample and send it to Virant Diagnostics to perform this test. The genetics laboratory will perform the genetic test and analyze the results which will be reviewed by a certified geneticist before they are reported back to your healthcare provider.

What do my High-Sensitivity *KIT* D816V Mutation Hotspot test results mean?

The High Sensitivity *KIT* D816V Mutation Hotspot reports the percentage of your DNA with the *KIT* D816V mutation. The percentage can be used to predict SM disease severity (a higher percentage indicates increased risk for disease), monitor the progression of the disease, and monitor your response to *KIT* D816V mutation therapy.

- Positive: A *KIT* D816V percentage of ≥ 0.015% is a positive result. Your healthcare provider may use this positive result to confirm a diagnosis of SM.
- Negative: A *KIT* D816V percentage of 0% is a negative result (patients with a mutated allele percentage of 0-0.005% will be detected as 0%). If your healthcare provider still suspects a diagnosis of SM, they will continue to monitor your condition. Repeat testing may be necessary if your symptoms worsen.

- Inconclusive: If the *KIT* D816V percentage falls within 0.005-0.015%, the results are inconclusive. The presence of the *KIT* D816V mutation cannot be confirmed and repeat testing should be performed with a new sample in 6 months.

How can I get MCD testing at Virant Diagnostics?

Consult your healthcare provider if you are experiencing MCD symptoms. They will review your symptoms and decide what testing is necessary for a diagnosis. You may suggest Virant Diagnostics for MCD genetic testing and direct them to our website (https://virantdx.com/) to learn more about our MCD genetic tests.

What if I am negative for HαT and SM?

If you do not meet the criteria for a diagnosis of HαT or SM, your healthcare provider may consider other MCDs:

- **What is cutaneous mastocytosis (CM)?**
  Cutaneous mastocytosis (CM) is a condition with too many mast cells in the skin. Patients with CM present with dark, hive-like skin lesions that are tan or brown and are more prone to severe allergic reactions. However, patients with CM are not affected in body parts other than the skin and therefore do not meet the criteria for SM.
- **What is mast cell activation syndrome (MCAS)?**
  Mast cell activation syndrome (MCAS) is a condition with recurring, severe anaphylaxis caused by mast cell mediators; however, patients do not meet the diagnostic criteria for SM, CM, or HαT.

How are MCDs treated?

Left untreated, MCD symptoms can lead to severe, life-threatening anaphylaxis. While there is no cure, MCD treatment focuses on reducing the frequency and severity of attacks. Patients should avoid known triggers and may be prescribed medication based on their differential diagnosis.

- Antihistamines (available over the counter, e.g., Benadryl®, Zyrtec®, Allegra®, Claritin®): block histamine activity
- Mast cell stabilizers (prescription medication): control mast cell activity
- Leukotriene inhibitors (available over the counter, e.g., Singulair®): block leukotriene (mast cell mediator) activity
- Aspirin therapy (under the supervision of a healthcare provider)
- Anti-IgE therapy
- Chemotherapy, including *KIT* D816V inhibitors when the mutation is detected (Avapritinib®)