Histamine Intolerance

How your genes impact your ability to break down histamine

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Genetic Lifehacks
Learn. Experiment. Optimize.

Do you deal with sinus drainage after you eat? Periodic itching and hives? Migraines, irritability, anxiety, brain fog? The weird and seemingly unrelated symptoms of histamine intolerance can drive you nuts trying to figure out the root cause.

Histamine intolerance is caused by an imbalance of too much histamine in the body that isn't balanced out by your capacity to break it down. Too much histamine can affect many different functions in the body, giving rise to many different symptoms seen in histamine intolerance. The imbalance of histamine can be caused by your body producing too much histamine or by not being able to properly break down histamine from foods. (Or both!)

How well your body breaks down histamine is partly determined by genetics:

- **Your genetic data** can help you figure out if your genes are contributing to your histamine intolerance.
- Knowing which genetic variants you carry can lead to **targeted solutions** that are more likely to work for you.

This ebook goes in-depth on the research into histamine intolerance. I'll include the genetic variants that impact histamine levels, and then go through solutions and options at the end. Everything is fully referenced, so you can easily dig into the research yourself.

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Classified as a *biogenic amine*, histamine is a molecule that plays many roles in the body. Histamine's many functions include:

- causes **allergic reactions**,
- acts within our **immune defense** system,
- dilates blood vessels (**vasodilatation**)
- acts as a **neurotransmitter**
- works as a **signaling molecule** in the stomach to release acid

While most of us think of histamine only during allergy season, **histamine is a vital part** of the way your body works.

What are the symptoms of histamine intolerance?

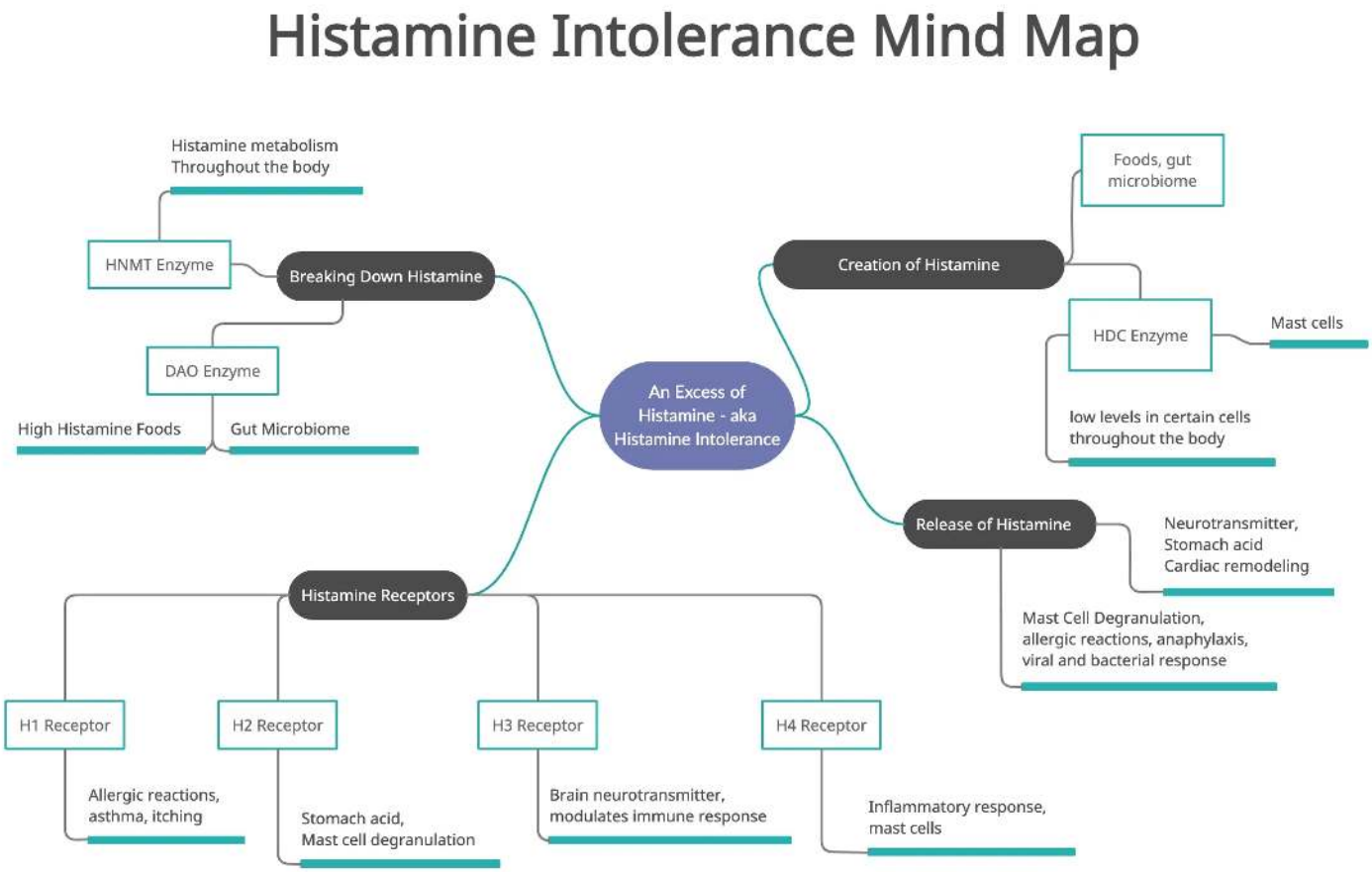
Histamine intolerance symptoms impact many different systems in the body, including[ref]:

- **Head:** headaches & migraines
- **Mood:** anxiety, irritability, brain fog
- **Stomach:** acid reflux, nausea, stomach pain
- **Intestines:** bloating, diarrhea, constipation
- **Heart:** heart arrhythmia, dizziness
- **Sinuses:** drainage, congestion
- **Skin:** hives, itching, flushing,
- **Sleep:** insomnia, early waking

People with histamine intolerance usually have **several of the symptoms** above, but they likely won't have **all** of the symptoms.[ref]

Historical note: Too much histamine has been known for decades to cause scombroid poisoning – the type of food poisoning from eating fish that isn't fresh.[ref]

Here's a visual overview of what we are going to cover here:



Causes of histamine intolerance:

The **two main causes** of histamine intolerance are:

- **not enough of the enzymes** needed to break down histamine (DAO and HMNT) – and/or-
- **too much histamine** being produced (gut microbes producing histamine, leaky gut, mast cells degranulating too easily, HDC variants, chronic exposure to allergens).

Breaking down histamine:

There are two ways that your body clears histamine: using the DAO enzyme or the HMNT enzyme.[ref]

1) Diamine oxidase (DAO) enzyme: Histamine from **foods or bacteria** in your gut is broken down or metabolized using the DAO (diamine oxidase) enzyme. The DAO enzyme is produced in the villi lining the small intestines and is released to metabolize histamine. [ref]

2) Histamine methyltransferase (HMNT) enzyme: The HMNT enzyme works throughout the body to deactivate and break down **histamine created by your body**. Thus, histamine that is used as a signaling molecule in the stomach or as a neurotransmitter in the brain will be broken down via a reaction that incorporates the HMNT enzyme.[ref]

Diamine Oxidase (DAO) enzyme:

Diamine oxidase is encoded by that AOC1 gene. It is mainly produced in the intestines in order to counteract histamine from foods and histamine created by intestinal bacteria. Foods that contain a lot of histamine include aged cheeses, aged meats, fermented foods, and more.

Certain bacteria in the gut (including those from some probiotics or fermented foods) can also increase histamine levels in the body. People with histamine intolerance show altered gut microbiome composition as well as elevated levels of zonulin, which regulates tight junctions in the intestines (leaky gut).[ref] A recent study of histamine intolerance patience found that they had “a significantly higher abundance of histamine-secreting bacteria…”[ref]

The DAO enzyme is also used by the body to break down other biogenic amines, including tyramine, putrescine, cadaverine, spermidine, and spermine. High levels of other biogenic amines can reduce the ability of DAO to break down histamine.[ref]

HMNT enzyme:

The HMNT enzyme is responsible for breaking down histamine in the central nervous system.

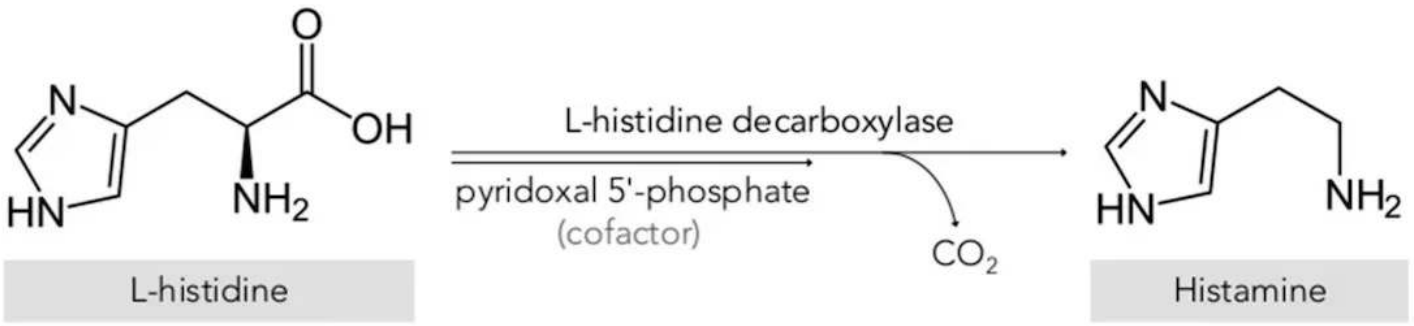
Recent studies show exactly how important HNMT is in **controlling brain histamine** levels. Genetic variants that change HNMT levels in the brain are linked to an increased risk of neurodegenerative disorders such as Parkinson's disease. Studies also link HNMT variants to an increased risk of migraines and ADHD.[ref] Rare mutations that inactivate the HNMT enzyme are linked to intellectual disability.[ref]

The HNMT enzyme acts throughout the body. Genetically decreased HNMT is also linked to atopic dermatitis or eczema. [ref]

Creation of Histamine:

Histamine is made from the amino acid histidine. It is an essential amino acid, which means that humans cannot make it in our bodies and must obtain it from diet. Histidine can be used in the body for several different purposes, including the production of histamine.

Histidine decarboxylase (HDC gene) is an enzyme that catalyzes the reaction of histidine into histamine. It does this inside various different cell types, including creating histamine in large amounts in mast cells.



histidine -> histamine (PMC7463562)

Not enough histamine:

Without enough histidine decarboxylase, animal studies show behavior that resembles Tourette syndrome.

Genetic studies show that people with Tourette's (vocal and motor tics) may have rare HDC gene mutations as a cause. The loss of histamine in the basal ganglia causes too much dopamine in that region of the brain, resulting in tics.[ref]

Too much histamine and the heart:

Histamine is also essential in the way that the heart muscle functions. Too much histamine here can be detrimental, and people with chronic heart failure have higher average plasma histamine levels. In fact, a genetic variant in the HDC gene that reduces histamine levels is linked to a significantly decreased risk of chronic heart failure.[ref] Additionally, clinical trials show that blocking the H2 receptor is beneficial for chronic heart failure. Famotidine (Pepcid AC) improved cardiac symptoms and ventricular remodeling.[ref][ref]

Histamine receptors explain the different effects of histamine

You may be wondering why one molecule can cause so many different actions in the body...

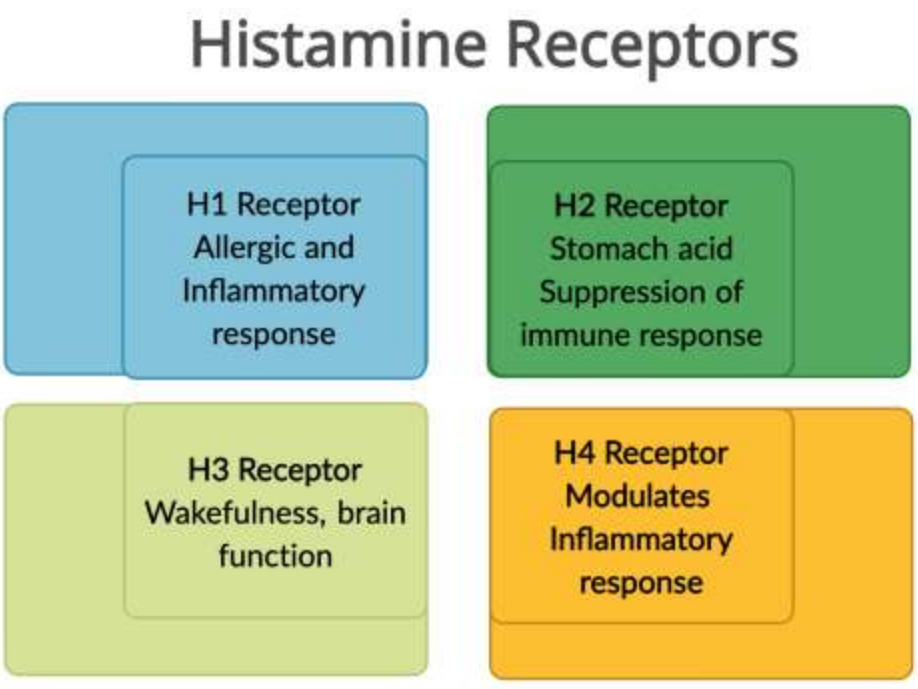
How can histamine cause headaches and heartburn and hives?

The function of histamine in a certain part of the body **depends on the receptor** it binds to.

Different histamine receptors are found in different parts of the body:[ref]

- **H1 receptors**: Found in smooth muscle, endothelial cells (lining the blood vessels), central nervous system, and mast cells. Activating the H1 receptors causes **allergy**-type symptoms such as itching, swelling, **vasodilation**, nose running, and skin reactions. H1 receptors are also important in **asthma** reactions.
- **H2 receptors:** When histamine activates the H2 receptors in the **stomach, acid** is released. H2 receptors are also found in the intestinal tract and the walls of blood vessels. **Mast cells** also have H2 receptors, which, when activated, cause the release of more histamine. In the heart, H2 receptors are important in controlling the rhythm.
- **H3 receptors:** The central and peripheral nervous systems contain H3 receptors, which act as a feedback loop for histamine levels in the **brain**. Activating the H3 receptors impacts serotonin, norepinephrine, and acetylcholine release.[ref]
- **H4 receptors**: These histamine receptors are at the core of the **inflammatory response**. H4 receptors are found in the bone marrow, basophils (a type of white blood cell), the thymus, small intestine, spleen, colon, and mast cells.[ref]

Three types of histamine receptors are found in the intestines: H1, H2, and H4. Interestingly, a study showed that people with **food allergies and IBS** had significantly **higher levels of H1 and H2 receptors** in their intestines.[ref]



Mast cells and histamine release

Mast cells are a type of immune cell that store histamine. They are found in most tissues in the body, especially in the areas of the body exposed to the outside world.

Allergens cause mast cells to burst (degranulate) and release histamine. Large numbers of mast cells are in the skin, bronchial tree mucosa, and intestinal mucosa. Viruses, bacteria, and fungi also activate mast cells.[ref]

Some think that histamine intolerance is a subset of mast cell activation syndrome (MCAS)

Related article: Mast cell activation syndrome

For more in-depth info on mast cells and histamine, check out Research Studies on Mast Cells and Histamine Intolerance, where I dive into all the different ways histamine can affect you.

Histamine, Sleep, and Circadian Rhythm:

Histamine acts in the brain as a neurotransmitter. It is an alerting neurotransmitter, rising in the morning hours to wake us up. About 50% of the histamine in the brain is from mast cells.[ref]

Benadryl, a commonly used antihistamine, has the side effect of making people sleepy. It is due to the actions of histamine in the brain.

Altering histamine levels in the brain changes sleep:

- In mice, knocking out the histamine receptors in the brain shows that it alters sleep patterns a little bit. Without histamine, mice were slower to wake up. They also had fragmented sleep and decreased non-REM sleep.[ref]
- In another animal study, researchers decreased the number of mast cells in the brain, reducing histamine production. It did not affect the amount of time that the mice slept overall, but it did affect their brain waves in sleep and their ability to bounce back after sleep deprivation.[ref]

In a recent study in people who had suspected histamine intolerance, the researchers found that about 1/4 of the patients had a circadian change in histamine levels that differed from a control group. These patients had significantly reduced DAO enzyme levels during the day and subsequently higher histamine levels.[ref]

Histamine Intolerance: Genetic Variants

Breakdown of histamine:

DAO (diamine oxidase) is the enzyme produced by the intestines, breaking down histamine from foods. The **AOC1 gene** codes for the production of the **DAO enzyme**. Genetic variants in AOC1 can increase or decrease the production of the enzyme.

Note that rare mutations influencing DAO production are not included with most genetic data, so the information below does not give you the complete picture.[ref][ref]

AOC1 gene: encodes diamine oxidase (DAO):

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][ref], increased risk of migraines due to histamine[ref]

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

- G/G: typical (most common genotype)
- 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** H645D (23andMe v4; AncestryDNA(older)):

- C/C: typical, high
- C/G: reduced production of DAO (35% reduction)
- G/G: reduced production of DAO (50% reduction)[ref]

Check your genetic data for **rs2071514** (23andMe v5; AncestryDNA):

- A/A: possibly higher DAO[ref]
- A/G: possibly higher DAO
- G/G: typical

HNMT genetic variants:

Histamine n-methyltransferase (HMNT) 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. HNMT is responsible for the elimination of 80% of histamine in the body.[ref]

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], higher histamine levels
- C/T: reduced breakdown of histamine compared to C/C
- C/C: typical[ref]

Check your genetic data for **rs2071048** -464(23andMe v4; AncestryDNA):

- T/T: increased risk of asthma (and higher histamine), common variant[ref]
- C/T: typical asthma risk
- C/C: typical asthma risk

Methylation Cycle:

The methylation cycle plays a role in breaking down monoamine neurotransmitters, including histamine. It is also important in creating the methyl groups needed for the HMNT enzyme to work. So looking at your methylation cycle genes can also help with balancing out histamine intolerance.

The MTHFR gene codes for an enzyme that is a key player in the folate cycle. It is one source of methyl groups for the methylation cycle. **Decreased enzyme activity of MTHFR – combined with a diet lacking in folate or choline – may cause a reduced breakdown of histamine.**

Check your genetic data for **rs1801133** (23andMe v4, v5; AncestryDNA):

- G/G: typical
- A/G: one copy of MTHFR C677T allele (heterozygous) decreased enzyme function by 40%
- A/A: two copies of MTHFR C677T (homozygous) decreased enzyme function by 70 – 80%

Check your genetic data for **rs1801131** (23andMe v4, v5; AncestryDNA):

- T/T: typical
- G/T: one copy of MTHFR A1298C (heterozygous), slightly decreased enzyme
- G/G: two copies of MTHFR A1298C (homozygous), decreased enzyme by about 20%

Creation of Histamine:

HDC gene: encodes the histidine decarboxylase enzyme, which is used in the conversion of histidine into histamine

Check your genetic data for **rs2073440** (23andMe v4, v5; AncestryDNA):

- T/T: typical
- G/T: Reduced HDC, decreased risk of allergic rhinitis (less histamine), reduced risk of chronic heart failure
- G/G: Reduced HDC, decreased risk of allergic rhinitis (less histamine)[ref] reduced risk of chronic heart failure[ref]

Check your genetic data for **rs267606861** (AncestryDNA only):

- C/C: typical
- A/C: carrier of a pathogenic mutation for Tourettes, reduced HDC (rare)[ref]

Histamine Receptors:

HRH1 gene: histamine receptor 1; this receptor is responsible for the allergy-type symptoms associated with histamine (nose running, eyes watering, itchy skin, airway reactivity)

Check your genetic data for **rs901865** (23andMe v4, v5; AncestryDNA):

- C/C: typical
- C/T: increased asthma risk (likely increased HRH1)
- T/T: increased asthma risk (likely increase HRH1)[ref]

HRH2 gene: histamine receptor 2, this receptor is active in the production of stomach acid, the sinus node of the heart, and other places in the body

Check your genetic data for **rs2067474** (23andMe v4, v5; AncestryDNA):

- A/A: Decreased HRH2; protective against chronic heart failure[ref],protective against gastric cancer[ref], lower risk of gastritis[ref]
- A/G: protective against chronic heart failure, protective against gastric cancer, lower risk of gastritis
- G/G: typical (more common genotype) higher HRH2, higher risk of CHF, gastritis

HRH4 gene: histamine receptor 4; found throughout the body, including in the brain. Histamine receptors are also important in cancer progression.

Check your genetic data for **rs11662595** (23andMe v4, v5; AncestryDNA):

- A/A: typical
- A/G: decreased HRH4 activation (receptor dysfunction), increased risk of progression in non-small cell lung cancer
- G/G: decreased HRH4 activation (receptor dysfunction), increased risk of progression in non-small cell lung cancer[ref]

Breaking down Tyramine:

The DAO enzyme also breaks down tyramine, another biogenic amine. Many of the same foods that are high in histamine are also high in tyramine.

People who are on MAOIs, a type of antidepressant, are at a higher risk of having problems with breaking down tyramine.

Tyramine is metabolized through three different pathways in the body: MAOA, CYP2D6, and FMO3. Check your genetic variants for tyramine intolerance here.

If you have variants in all three pathways, please read the full article on tyramine intolerance. This may be exacerbating problems with histamine via using the same DAO enzyme.

Lifehacks for histamine intolerance:

Below are the research-backed solutions for histamine intolerance. You may need to try several different 'lifehacks' to see which works best for you.

A Low-histamine diet, at least initially:

A low-histamine diet restricts foods that contain high levels of histamine or that cause the body to release histamine. To experiment with a low-histamine diet, eliminate all of the higher histamine foods for a period of time to see how your body responds.

In general, foods that are fermented or aged are higher in histamine. A quick overview of high histamine foods includes processed meats, cheeses (except farmers cheese), fish and seafood that isn't completely fresh, spinach, chocolate, tomatoes, strawberries, wine, sake, and more.

If you are considering a low histamine diet, I find this **histamine food list** to be the most thorough: **Complete list of foods that are high in histamine (pdf).**

What does a low-histamine diet do?

- Decreasing the amount of histamine you take into your body will lower the overall amount of histamine circulating in your body.
- Research studies show that a low histamine diet helps with chronic urticaria (itchiness, hives), migraines, stomach problems, and asthma.[ref][ref]

Should you maintain a low histamine diet long-term?

Trying a low-histamine diet for a period of time can give you a lot of insight into how histamine affects your body, but it may not be a diet you want to continue long-term. A low-histamine diet restricts many healthy foods that you may enjoy, such as spinach, strawberries, and avocados.

Use a low histamine diet as a tool to learn which histamine-containing foods bother you the most. It can also be a short-term way of getting histamine responses under control.

Low FODMAPs diet: histamine and gut problems

Interestingly, a randomized controlled study for people diagnosed with IBS found that a low FODMAPs diet reduced symptoms and reduced histamine levels. It could mean that a FODMAPs diet works because IBS is related to histamine intolerance – or – could mean that the people diagnosed with IBS were really dealing with gut-related histamine symptoms.[ref] Additionally, the low FODMAPs diet may be helping to decrease intestinal barrier permeability.

A low FODMAPs diet cuts out a lot of high histamine foods, so it could reduce histamine levels through eating fewer foods high in histamine. On the other hand, a low FODMAPs diet impacts the gut microbiome and histamine-producing bacteria. Animal studies also link IBS to mast cell activation in the colon, so changing the gut microbiome with a FODMAPs diet may also impact colonic mast cells.[ref]

Learn more about what is included in a low FODMAPs diet: Starting a Low FODMAPs diet

Vitamins & Natural Supplements for Histamine Intolerance:

Vitamin B6 is a cofactor in the reactions that degrade histamine. Pyridoxal-5'-phosphate is the active form of vitamin B6. Foods high in vitamin B6 include salmon, tuna, eggs, milk, beef, and carrots. (article) Not sure if you get enough vitamin B6? Cronometer.com is a free online app where you can record the foods you eat each day to determine the nutrient content – and it includes the vitamin B6 content of foods.

Quercetin has also been shown in studies to inhibit mast cells from degranulating. Mast cells are one way that the body releases histamine.[ref]

Fisetin, another natural flavonol, has been shown in cell studies to inhibit mast cells from degranulating.[ref][ref][ref](Read more about fisetin)

Luteolin has been shown in studies to inhibit histamine release from mast cells.[ref]

There are **DAO supplements** available that may help some people who don't produce enough of the enzyme. A recent study found that histamine intolerance symptoms improved significantly when taking DAO capsules before meals.[ref]

Looking for an alternative to expensive DAO supplements? **Pea shoots** – those first few inches of the pea plant that come up in the spring – are naturally high in the **DAO enzyme**.[ref] You can easily grow pea shoots at home, and they are a tasty addition to a salad.

Gluten sensitivity and histamine intolerance

A new study looked at the correlation between symptoms of histamine intolerance and gluten intolerance. It concluded that there was a significant overlap in symptoms and that **a low histamine diet may help people with gluten sensitivity.**[ref]

Food preparation methods to reduce histamine levels

How food is prepared makes a big difference in the histamine levels.

A recent study concluded, "**Frying and grilling increased histamine** levels in foods, whereas boiling had little influence or even decreased it. The boiling method might be helpful to control the effect of histamine in histamine-sensitive or susceptible patients, compared with frying and grilling."[ref]

Additionally, **leftovers** kept in the fridge (especially meats!) can build up histamine. Instead, try putting your leftovers in the freezer and thawing them when you want to eat them. Histamine levels increase as food starts to break down. Additionally, other biogenic amines increase, which shuttles part of your DAO enzyme production towards breaking down the other biogenic amines.[ref]

Fermenting and drying foods also increase histamine levels.

Reducing histamine levels in food:

Here are a few tips on reducing histamine levels in your foods:

- Avoid leftovers that have been sitting in the fridge for a few days.
- Freeze meat when you bring it home from the grocery store; quick thaw it on the day you eat it.
- Look for fish or seafood that says “frozen at sea” on the package
- *S*moked meats, such as BBQ pork or brisket, can contain very high levels of histamine. Sometimes it is worth it, and sometimes it isn’t… you decide.
- Foods cooked in a crockpot (low and slow) are more likely to be high in histamine.

Plan ahead:

- If you’re eating out and don’t know how fresh the meat is, take a DAO supplement or quercetin before your meal.
- If you ate pepperoni pizza for dinner (knowing that you’ll regret it :-), take an H2 blocker before bed to prevent heartburn.
- During pollen season, you may find that sticking to a low histamine diet helps to reduce your allergy symptoms.

One OTC medication that can help to reduce histamine levels is Benadryl. It isn’t something that I would take on a daily or long-term basis, though, since it is linked to an increased risk of dementia. But it is a medication that I keep on hand, especially when traveling. Benadryl gel caps come in a dye-free version that doesn’t include red dye, which is in the tablets.

H2 blockers, such as Tagamet and Pepcid AC, may help if you have histamine-related stomach problems. Again, these OTC medications aren’t something that I personally would want to take daily, but rather something to have on hand when needed.

Chemical triggers of histamine release:

- "Calcium triggers the secretion of histamine from mast cells **after previous exposure to sodium fluoride**."[ref] *The addition of sodium fluoride to drinking water is common in most US municipalities.*
- **PFOAs** (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-α, IgE, and IgG1 in the ovalbumin-induced systemic anaphylaxis. The present data indicate that PFOA aggravated FcεRI-mediated mast cell degranulation and allergic symptoms."[ref] You will find PFOAs in Teflon, stain-resistant carpeting, microwave popcorn bags, food wrappers, etc.
- Off-gassing from carpeting may cause mast cell release in the case of sick building syndrome.[ref]
- **Sodium benzoate,** a common preservative, causes histamine release in people with allergies and asthma.[ref]
- For some people, **aspirin** and other salicylates can cause histamine problems – possibly through basophil activation.[ref]
- The food additive **Polysorbate 80** causes histamine release.[ref] Polysorbate 80 is in most brands of pickles — except organic pickles.

Medications that decrease DAO enzyme production

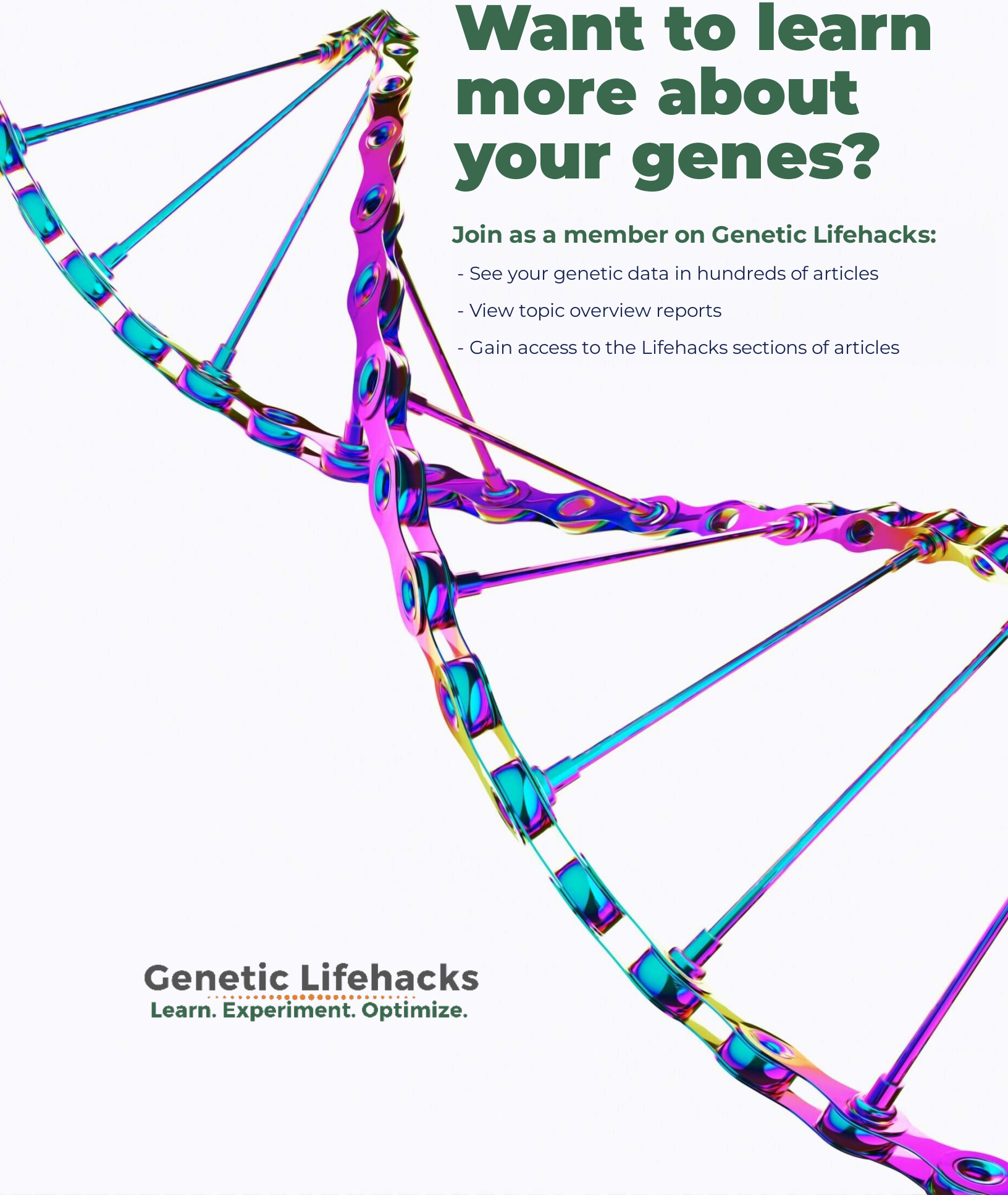
In addition to foods, **drug interactions can cause a decrease** in DAO enzyme production.

- **Metformin** has been shown to decrease the DAO enzyme.[ref]
- Vitamin B3 (**nicotinamide or niacinamide**) may increase histamine levels at doses of 100 mg or higher.[ref]

Conclusion

High histamine levels can cause a variety of symptoms, depending on which receptor it acts on. The wide variation in symptoms can make it hard to diagnose. Often, a trial period of a low-histamine diet can help you to pinpoint whether high histamine levels are at the root of your symptoms.

Genetics plays a role in susceptibility, but other factors such as mast cell activation or chronic allergies also comes into play. Additionally, the gut microbiome can add to histamine issues, especially when taking probiotics that produce more histamine.



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