Lifecode GX ®
— Professional Genotype Analysis —

Histamine Intolerance

Report for Vaness Kimbell (CP00096235)

Histamine is a chemical that is released by white blood cells into the bloodstream when the immune system is defending against a potential allergen. This release can result in an allergic reaction from triggers such as pollen, mold, and certain foods.

Histamine has many important and diverse biological functions: it protects against infection, regulates physiological functions in the gut, and acts as a neurotransmitter.

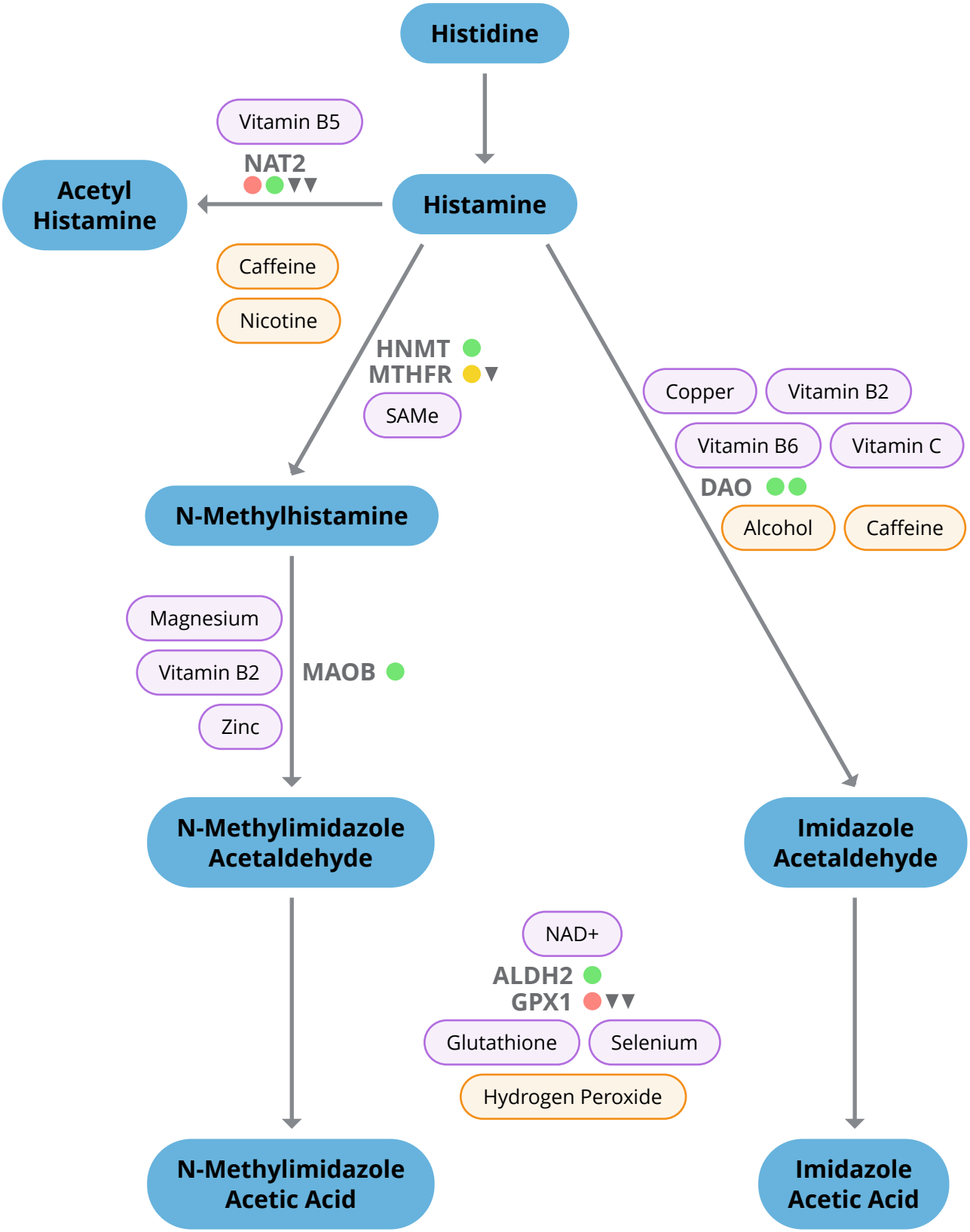
Once formed, histamine is either stored or rapidly inactivated by its primary degradative enzymes - diamine oxidase (DAO) in the gut, and histamine-n-methyltransferase (HNMT) in the nervous system and lungs. Histamine degradation is altered by genetics and environmental factors. Impaired histamine degradation can result in histamine toxicity and numerous symptoms that mimic an allergic reaction:

- **Skin:** itchiness, redness, rash, eczema, hives
- **Gastro-intestinal tract:** stomach acid reflux, diarrhoea, nausea, vomiting
- **Respiratory:** runny nose, broncho-constriction, asthma, chronic cough, nasal congestion
- **Vascular:** vasodilation, low blood pressure, dizziness, fainting, rapid heart beat, oedema, migraine/headaches
- **Neurological:** insomnia, anxiety, memory and concentration problems, ADHD

Because of its multifaceted symptoms, histamine intolerance is frequently underestimated, or its symptoms misinterpreted as they are often mistaken for a food allergy or a gastrointestinal disorder.

This report describes the genes, nutrients, and lifestyle and environmental factors that can impact histamine degradation. It provides a personalised summary pathway and detailed results, followed by a generic histamine intolerance guide.

Histamine Intolerance



Detailed Results

ALDH2 rs671	GG	No impact on acetaldehyde metabolism. ALDH2 is the second enzyme of the major oxidative pathway of alcohol metabolism and is also needed to breakdown the amine neurotransmitters. Support ALDH2 by limiting alcohol consumption, and increasing cofactors - vitamins B2 and B3, magnesium, molybdenum and zinc.
DAO rs10156191	CC	Normal DAO activity, normal degradation of histamine. Support DAO with vitamin B2, as it uses FAD as a cofactor.
DAO rs1049793	CC	Normal DAO activity, normal degradation of histamine. Support DAO with vitamin B2, as it uses FAD as a cofactor.
GPX1 rs1050450	AA ▼▼	Lower GPX1 activity and ability to break down the toxin hydrogen peroxide resulting from histamine metabolism. Increased intake of antioxidants, particularly glutathione and selenium may be beneficial to protect against histamine intolerance.
HNMT rs11558538	CC	No variance. No reported impact on HNMT activity or effect on histamine metabolism. Support HNMT with B vitamins, zinc and magnesium.
MAOB rs1799836	TT	Normal MAOB activity, normal breakdown of histamine metabolites in the HNMT pathway. Support MAOB with vitamin B2, magnesium and zinc.
MTHFR rs1801133	AG ▼	Reduced gene function impacting levels of 5-MTHF (methyl-folate) and subsequently SAMe, which is needed to support HNMT degradation of histamine. Methylation and histamine status are often inversely correlated. Methylation (and HNMT activity) can be supported by increasing intake of folate (green leafy vegetables) and other methylation promoting nutrients - B vitamins, vitamin C, zinc, copper and methionine (found in meats, fish, eggs, nuts and beans).

Detailed Results (continued)

NAT2 rs1041983	CC	Normal (fast) NAT2 acetylation activity. Not associated with slower histamine degradation to acetylhistamine. Support NAT2 with vitamin B5 as it uses the coenzyme A as a cofactor.
NAT2 rs1801280	CC ▼▼	Slower NAT2 acetylation activity, slower histamine degradation to acetylhistamine. May give rise to unpleasant symptoms such as abdominal discomfort, headache, runny nose, and itching. Support NAT2 with vitamin B5 as it uses the coenzyme A as a cofactor.

A Guide to Histamine Intolerance

This guide contains detailed explanations of the genes involved in Histamine Intolerance.

Histamine is a biological amine that is synthesised from the amino acid histidine by L-histidine decarboxylase (HDC) and requires vitamin B6 as a cofactor.

Histamine is synthesised by and stored predominantly in mast cells - in tissue, but also in basophils and platelets in the blood, neurons - in the nervous system and enterochromaffin-like (ECL) cells in the gut.

Once formed, histamine is either stored or rapidly inactivated by its primary degradative enzymes - diamine oxidase (DAO) in the gut and histamine-n-methyltransferase (HNMT) in the nervous system and lungs.

Histamine intolerance is a toxic response by the body resulting from an imbalance between accumulated histamine and the capacity to break it down. It seems to occur mainly as a result of impaired DAO activity either due to gastro-intestinal disease or through inhibition of DAO, by 'blockers' such as alcohol, black tea, green tea and medications. There is also evidence for a genetic predisposition in a subgroup of people with histamine intolerance.

Triggers are heterogeneous and differ greatly between individuals. The most common ones are:

- Ingestion of histamine-rich food, or of alcohol or drugs which release histamine or inhibit DAO
- Gastro-intestinal injury due to 'leaky gut', SIBO (small intestinal bacterial overgrowth), Crohn's or other IBDs, coeliac disease or infections such as H. Pylori
- Chronic stress and increased HPA (hypothalamic-pituitary-adrenal axis) activity which activates mast cells and increases histamine release
- Genetic predisposition due to variants on the DAO and/ or HNMT genes which reduce activity of the enzymes that break down histamine.

Histamine is primarily metabolised by two major pathways - DAO, and HNMT. The main DAO metabolite, acetaldehyde, is then oxidised to acetic acid by ALDH2, whilst the N-methyl-histamine product of the HNMT pathway is broken down by MAOB, which is then oxidised by ALDH2 too. NAT2 is an alternative pathway that converts histamine into acetylhistamine, which is then excreted in the urine.

Histamine Intolerance Genetics

The DAO gene - which is also known as AOC1 or ABP1 - produces the main enzyme for the metabolism of ingested putrescine, histamine and related compounds. The enzyme uses Flavin Adenine Dinucleotide (FAD) produced from Vitamin B2 as a cofactor. Variants on DAO may down-regulate enzyme activity, resulting in excess histamine and causing symptoms mimicking an allergic reaction. Alcohol is one of the most harmful products for people with DAO deficiency. It simultaneously releases endogenous histamine and blocks DAO activity, even in people not predisposed to low DAO levels.

HNMT controls the neurotransmitter activity of histamine in the brain and plays an important role in regulating the airway response to histamine. Variants have been reported to increase susceptibility to asthma. HNMT inactivates histamine via methylation - using SAMe as the methyl donor - therefore genetic variants that impact methylation (such as MTHFR) may also affect HNMT activity. The resultant N-Methylhistamine is then oxidatively deaminated to N-methyl-imidazole acetaldehyde by MAOB.

The MTHFR gene is responsible for making the protein methylenetetrahydrofolate reductase (MTHFR), the rate-limiting enzyme in the methylation cycle which catalyses the conversion of folate to 'active' folate (5- MTHF) needed to support the re-methylation of homocysteine to methionine, DNA synthesis and repair (vital for healthy cell division), and the synthesis of neurotransmitters, phospholipids and of SAMe (cofactor for methylation of histamine). Variants on the MTHFR gene usually result in lower enzyme activity. The C677T variant, which occurs in about 30% of people, can result in significantly reduced 5-MTHF levels - up to 40% reduction for heterozygotes and 70% for homozygotes (AA). MTHFR activity can be supported by increasing the intake of folate (B9) and the cofactors riboflavin (vitamin B2) and niacin (vitamin B3).

MAOB is a member of the monoamine oxidase gene family whose enzymes catalyse the deactivation of monoaminergic neurotransmitters. It is the main catalyst for the breakdown of phenethylamine (PEA), benzylamine and histamine. It also metabolises dopamine, tyramine and tryptamine, equally with MAOA. MAOB is located on the X chromosome, so males only carry one allele, inherited from their mother. We report results for males as homozygous as they will not inherit a 'balancing' allele. Variants on the MAOB gene are associated with reduced enzyme activity and slower breakdown of neurotransmitters and histamine.

Aldehyde dehydrogenase (ALDH2) belongs to the aldehyde dehydrogenase gene family. There are two major forms of ALDH in the liver: cytosolic ALDH1 and mitochondrial ALDH2. Most Caucasians have both forms, while approximately 50% of East Asians have the cytosolic but not the mitochondrial form. ALDH2 is the second enzyme of the major oxidative pathway of alcohol metabolism and is also needed to break down the amine neurotransmitters. A higher frequency of acute alcohol intoxication among Asians could be related to the absence of an active form of mitochondrial ALDH2.

GPX1 belongs to the glutathione peroxidase family, members of which catalyze the reduction of hydrogen peroxide (H2O2) by glutathione, limiting H2O2 accumulation, and thereby protecting cells against oxidative damage. It is also a selenoprotein, requiring the mineral Selenium. Variants on GPX1 may lower GPX1 activity and ability to break down the toxin hydrogen peroxide resulting from histamine metabolism by MAOB.

NAT2 encodes a type of N-acetyltransferase. The NAT2 isozyme functions to both activate and deactivate arylamine and hydrazine drugs, and carcinogens. Variants in this gene are responsible for the N-acetylation polymorphism in which human populations segregate into rapid, intermediate, and slow acetylator phenotypes. A slower NAT2 acetylation activity may lead to slower histamine degradation to acetylhistamine, which may give rise to unpleasant symptoms such as abdominal discomfort, headache, runny nose, and itching. Support NAT2 with vitamin B5 as it uses the Coenzyme A as a cofactor.

Nutrition and Lifestyle

Digestive Health

Heal the gut! Poor digestive health can impair DAO activity and enable free histamine to leak directly into the bloodstream.

Medication

Assess your response to medications associated with low DAO activity including the common painkillers ibuprofen and aspirin, antidepressants, antihistamines and antibiotics.

Environmental Allergens

Remove exposure to environmental and chemical allergens that may trigger a histamine release - such as cleaning products, cosmetics, dust mites, animal fur and dander.

Stress

Stress - whether physiological or emotional - triggers histamine release. Techniques such as Buteyko (breath control), yoga and meditation may help manage stress levels and stress response.

Alcohol

Eliminate or reduce alcohol intake particularly if you are susceptible to low DAO.

Reduce or avoid foods that are high in histamine

- Eliminate or reduce alcohol intake particularly if you are susceptible to low DAO
- Fermented products: sauerkraut, pickles, vinegar, fermented soy, yeast, yoghurt, kefir and aged cheese
- Alcohol - especially red wine - and champagne, white wine and beer
- Smoked, cured or fermented meats - sausage, pepperoni and salami
- Some fruits - strawberries, pineapple, bananas and kiwi and citrus fruits - as these are histamine liberators
- Some vegetables - spinach, tomatoes and aubergine
- Fish (frozen/smoked or canned) - mackerel, herring, sardines and tuna

Increase low histamine, antioxidant and anti-inflammatory foods

- Berries (goji, blueberries, cranberries, blackberries), pecan nuts, and quercetin (anti-oxidants)
- Green leafy vegetables (apart from spinach) - broccoli, bok choy, cucumber - and leafy herbs which are rich in B vitamins
- Other anti-inflammatory foods - celery, beetroot, fresh salmon, bone broth, walnuts, coconut oil, turmeric, ginger and apples
- Freshly cooked, organic, grass fed meats
- Gluten free grains - rice, quinoa, corn and millet
- Water - filtered/real fruit flavoured water

Follow-up and Testing

Diagnosis of histamine intolerance is set by presentation of two typical symptoms of histamine intolerance and improvement by histamine-free diet and antihistamines. Keep a diary of what food you eat, which medicines you take and other possible triggers and the symptoms you experience. Eliminate the suspected food and other triggers, then experiment with re-introducing them and monitoring for adverse reactions.

Speak to a health professional about clinical testing such as:

- High histamine levels
- Low DAO activity
- Food allergy testing (IgE). For example peanut allergy.
- Food sensitivity testing (IgG). For example gluten sensitivity.
- Food intolerance testing (including genetic testing). For example lactose intolerance.
- Adrenal stress profile test - a measure of stress and adrenal function.
- High tryptase - a marker for mast cell activation syndrome (MCAS). People who have this syndrome might have a hard time pinpointing the exact thing that triggers allergic reactions. Your doctor might test for tryptase, histamine, and prostaglandin levels, but there are no definitive tests. As histamine intolerance is a subset of MCAS, genetic testing of histamine intolerance could be helpful to pinpoint some MCAS symptoms, showing where genetic disruptions occur and how to support optimal function.

How to Read the Report

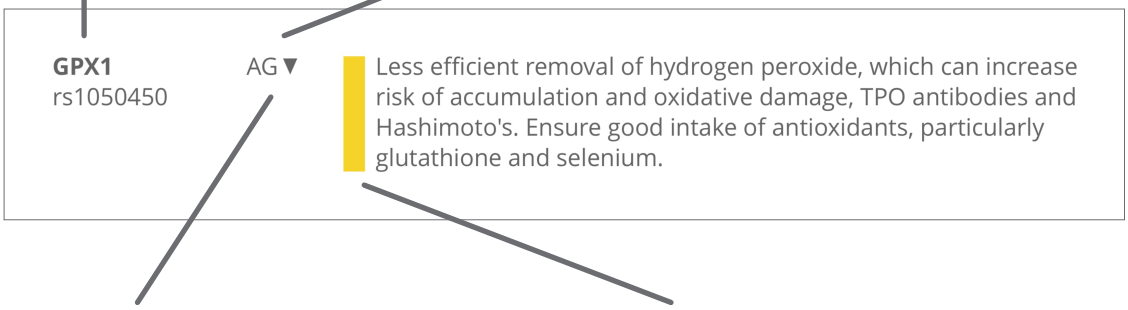
Genes

Results are listed in order of the gene short name. The 'rs' number is the reference sequence number that identifies a specific location on the genome. It is also known as a SNP (Single Nucleotide Polymorphism) pronounced 'snip', polymorphism or mutation.

Personalised Result

Your genotype result is shown as two letters (A,G,T or C) which represent the DNA bases present at that location.

Multiple attempts are made to achieve the required level of statistical confidence, but if that cannot be met it is reported as **'No result'**.



Arrow Direction

The direction of the arrow indicates the potential effect of the SNP on gene expression, where applicable - it can increase or decrease activity, or neither.

▲ up-regulates or increases the activity and effect on the gene

▼ down-regulates or decreases the activity and effect on the gene

No arrow - no effect on the activity of the gene

Highlight Colour

The genotype result highlight indicates the potential effect of the SNP on gene function in a particular context.

RED the effect of the variant is negative

AMBER the effect of the variant is somewhat negative

GREEN no variation, or the effect of the variant is positive

Pathway Diagram Key

Cofactor Inhibitor

References

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HNMT Histamine N-Methyltransferase

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MAOB Monoamine Oxidase B

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MTHFR Methylenetetrahydrofolate Reductase (NAD(P)H)

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