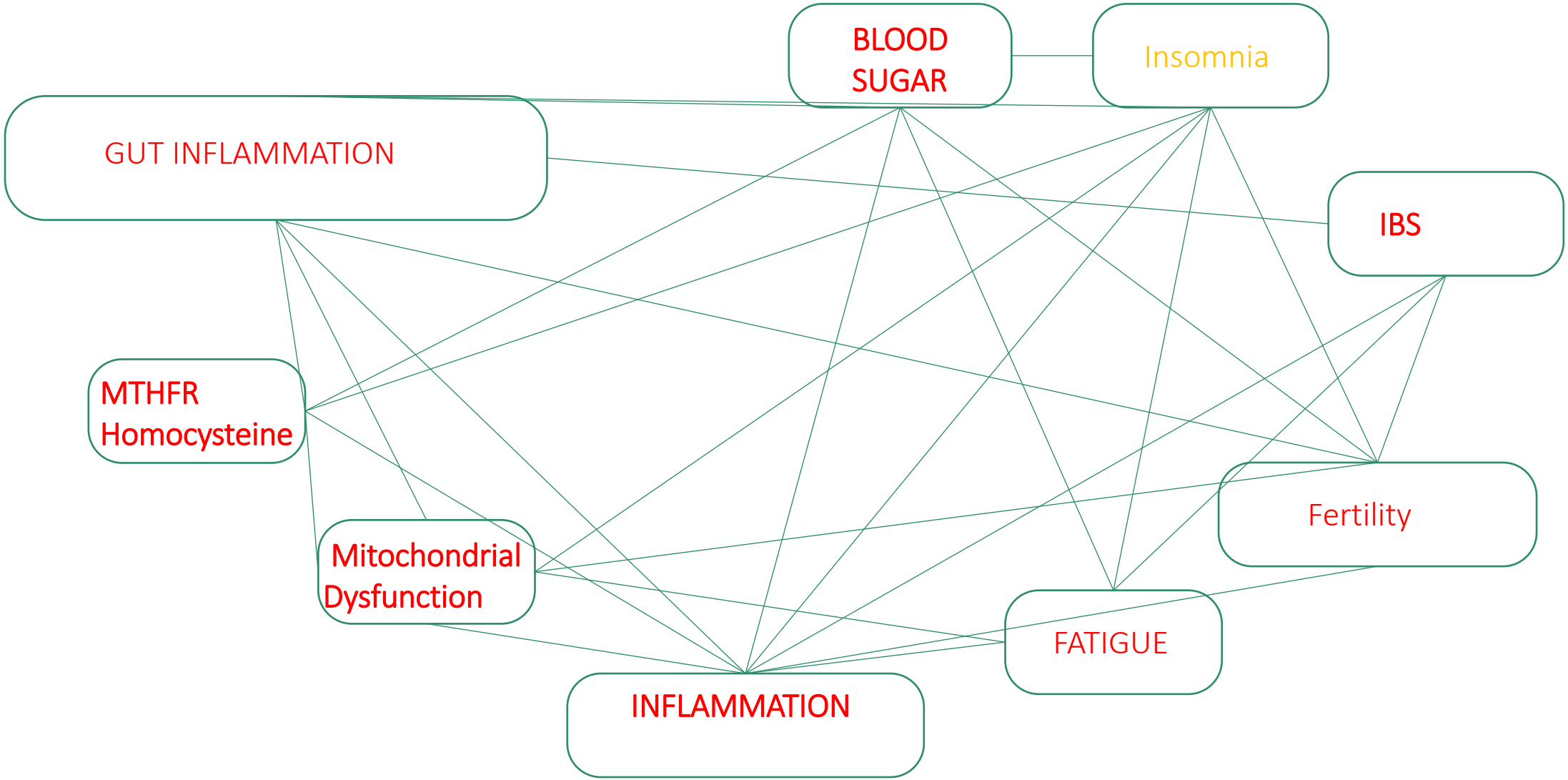
## Overall Artificial Intelligence (AI) Polygenic score and associated areas of concern

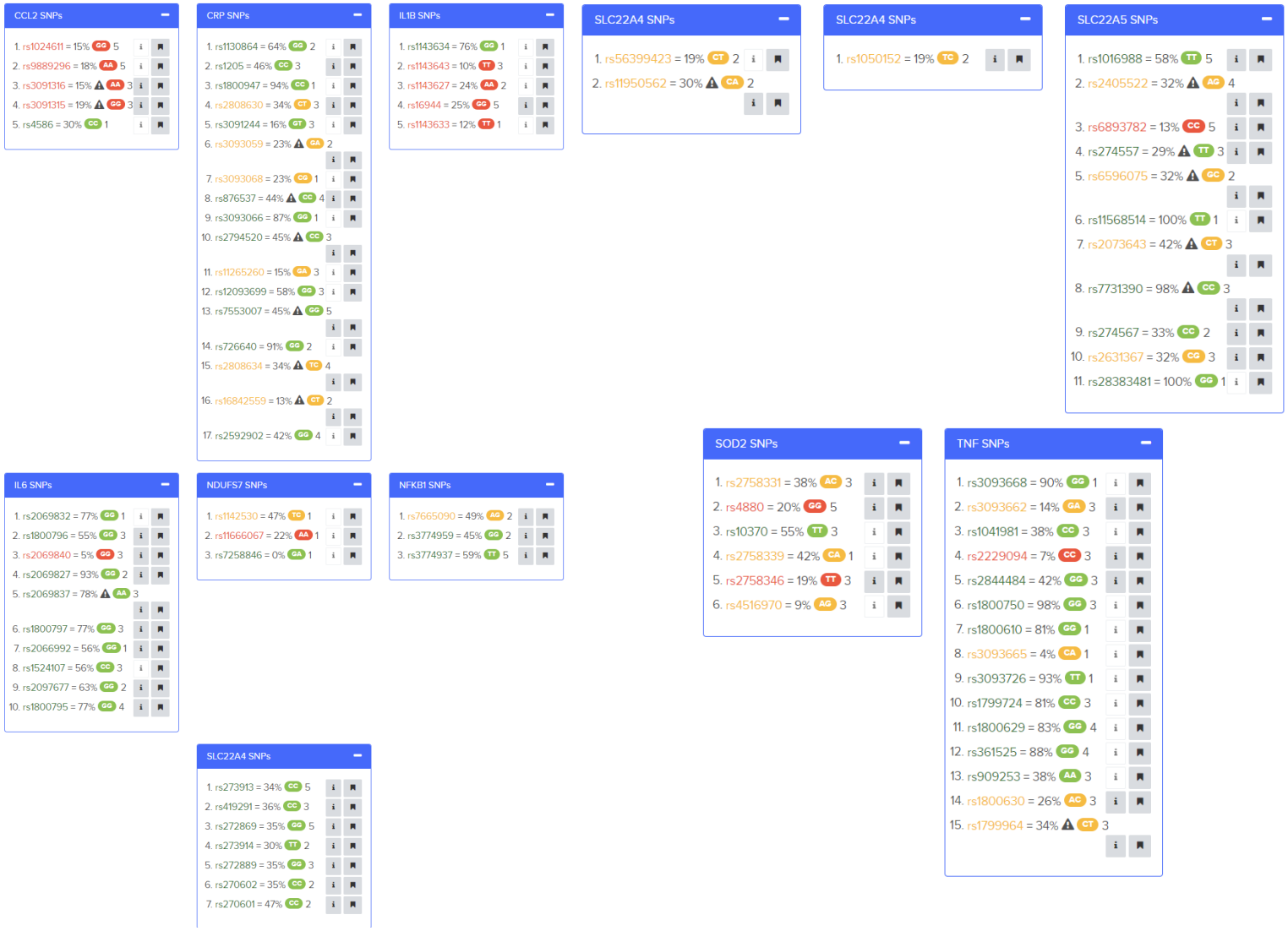
- INFLAMMATION 98th (worst 2% of the overall population)
- BLOOD SUGAR 81ST
- IBS 72nd
- INSOMNIA 62ND
- FATIGUE 61ST
- GUT INFLAMMATION 58TH

Dr. Valerio Vittone



# Core Inflammatory genes, NF-KB, IL6, CRP, CCL2, IL1B, TNF, Inflammasome activation & Oxidative stress & Mitochondrial damage

Dr. Valerio Vittone




- **SOD2 rs4880**

**Mechanism:**

•Overall, the evidence **points to lower enzyme activity for GG (R). SOD2 or MnSOD** was 33% higher in GA or AA compared to GG.(R) GG resulted in 39% lower SOD2 activity in red blood cells of 231 young adults (R) and human liver cells(R).

**The G allele is associated with:**

•GG were 70% more likely to get prostate cancer and 2.7X more likely to have a high grade prostate tumor. (R)

•However, people with GG had on average catalase activity of 18.1 k/g Hb higher than AA (Median= 86.3) (R).

•GG had more oxidative stress. (R)

•The G allele isassociated with Alzheimer's disease. (R)

•Alcoholics with GG had less gray matter. (R)

•GG is at greater risk for noise induced hearing loss. (R) AG is also at a higher risk of Noise induced hearing loss (R,R2,R3).

•Having a G allele makes you 3X more likely to have ear toxicity from cisplatin, a chemotherapy drug (R).

•GG had 2X greater risk of infertility in Chinese population and had high levels of sperm DNA damage and infertility(R).

•GG were less capable of handling Pthalates (R).

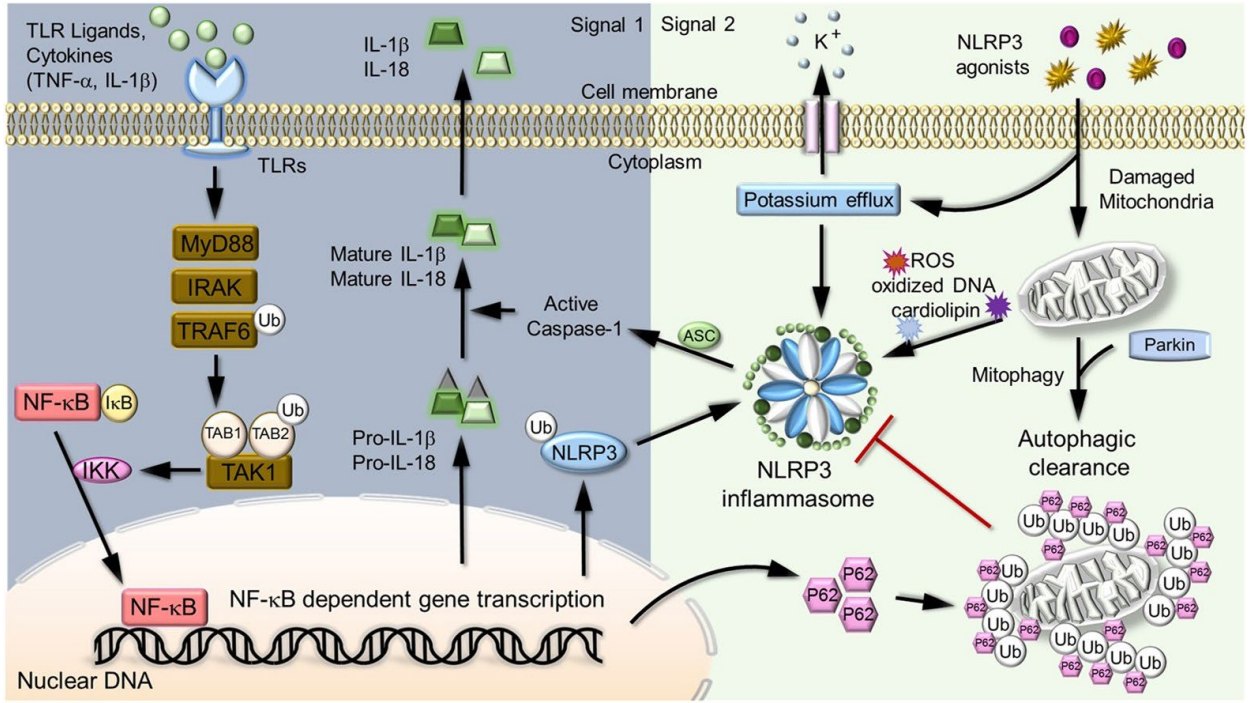
•Men with GG who had low long-termLycopene levels had a higher risk of aggressive prostate cancer. These results are consistent with findings from earlier studies that reported when antioxidant status is low, GGmay be associated with an increased risk of aggressive prostate cancer. (R)

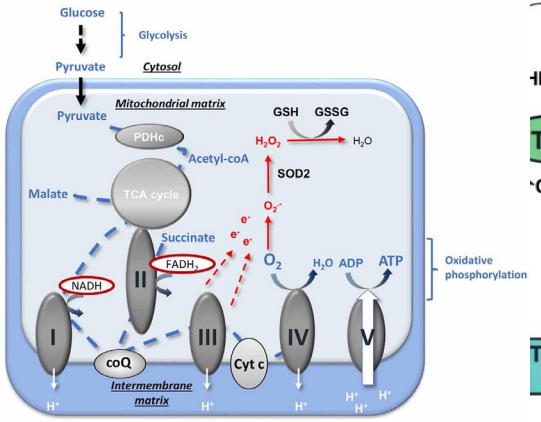
•GG or GAwas a risk factor for lower gray matter volume in alcoholics below the median alcohol consumption (p=0.03) but not in alcoholics above this level. (R)

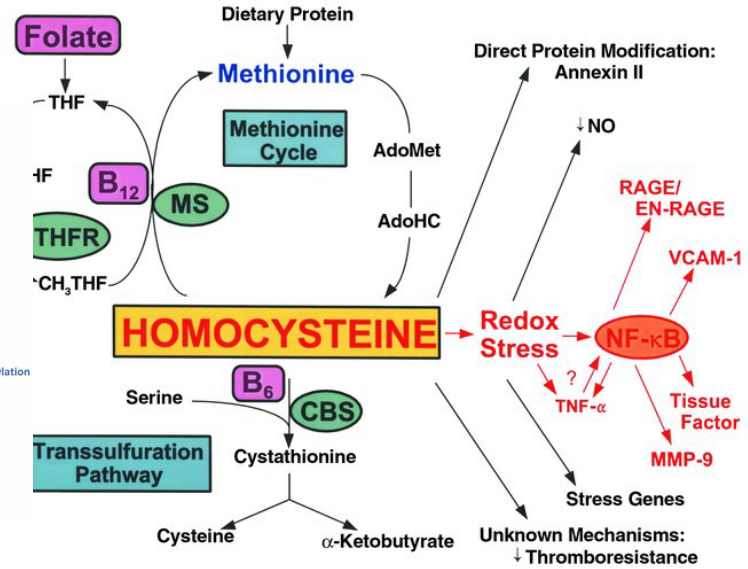
# Mitochondrial functions and inflammatory mediators activating NF-Kb and Inflammasome

The **chemokine (C-C motif) ligand 2** (CCL2) is also referred to as **monocyte chemoattractant protein 1** (MCP1) and **small inducible cytokine A2**. CCL2 is a small cytokine that belongs to the CC chemokine family. CCL2 recruits monocytes, memory T cells, and dendritic cells to the sites of inflammation produced by either tissue injury or infection.[3][4]

**NDUFS7 : NADH dehydrogenase [ubiquinone] iron-sulfur protein 7, mitochondrial**, also knowns as **NADH-ubiquinone oxidoreductase 20 kDa subunit**, **Complex I-20kD (CI-20kD),** or **PSST subunit** is an enzyme that in humans is encoded by the *NDUFS7* gene.[5][6][7] The NDUFS7 protein is a subunit of NADH dehydrogenase (ubiquinone) also known as Complex I, which is located in the mitochondrial inner membrane and is the largest of the five complexes of the electron transport chain.[8]

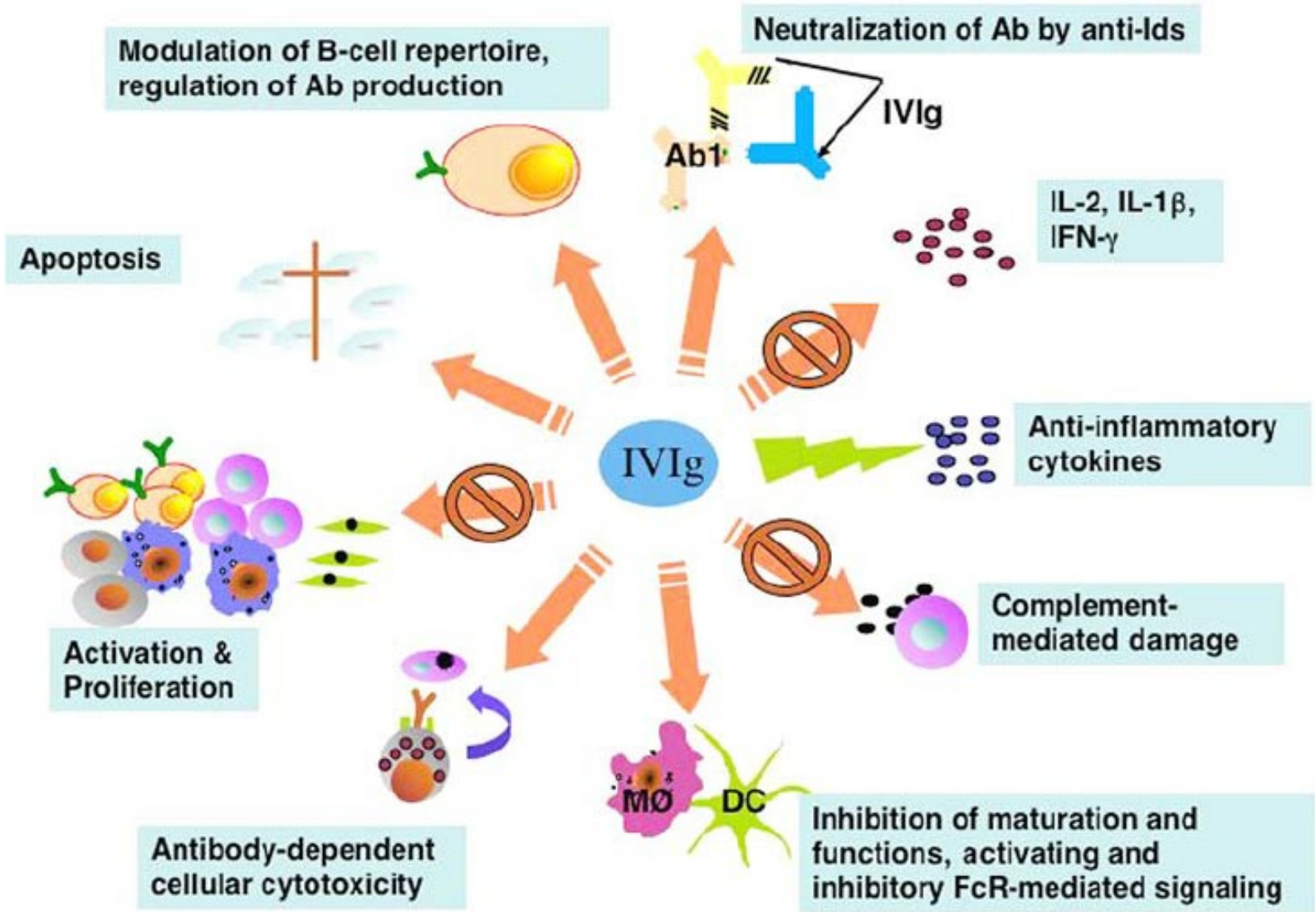


# IVIG Treatment benefits to decrease inflammatory response esp IL1-B etc





# Vitamin D metabolism, transport, VDR and GC (Vitamin D Binding Protein)


- **CYP2R1** is an enzyme responsible for the first step in converting vitamin D to its active form. It converts both vitamin D2 and D3 into the intermediary, inactive form of vitamin D (25-hydroxyvitamin D) in the liver. A mutation in this gene has been associated with selective 25-hydroxyvitamin D deficiency.
- **rs2060793 AA = lower levels of vitamin D, due to a diminished capacity to convert vitamin D3 to 25-hydroxyvitamin D** [R].

- **The GC gene** codes for the vitamin D-binding protein (DBP). **DBP can bind and transport many forms of vitamin D throughout the body [R].**
- GC variants may influence blood levels of vitamin D [R, R, R].
- **rs7041 CC/CA = less of a response to vitamin D [R].**

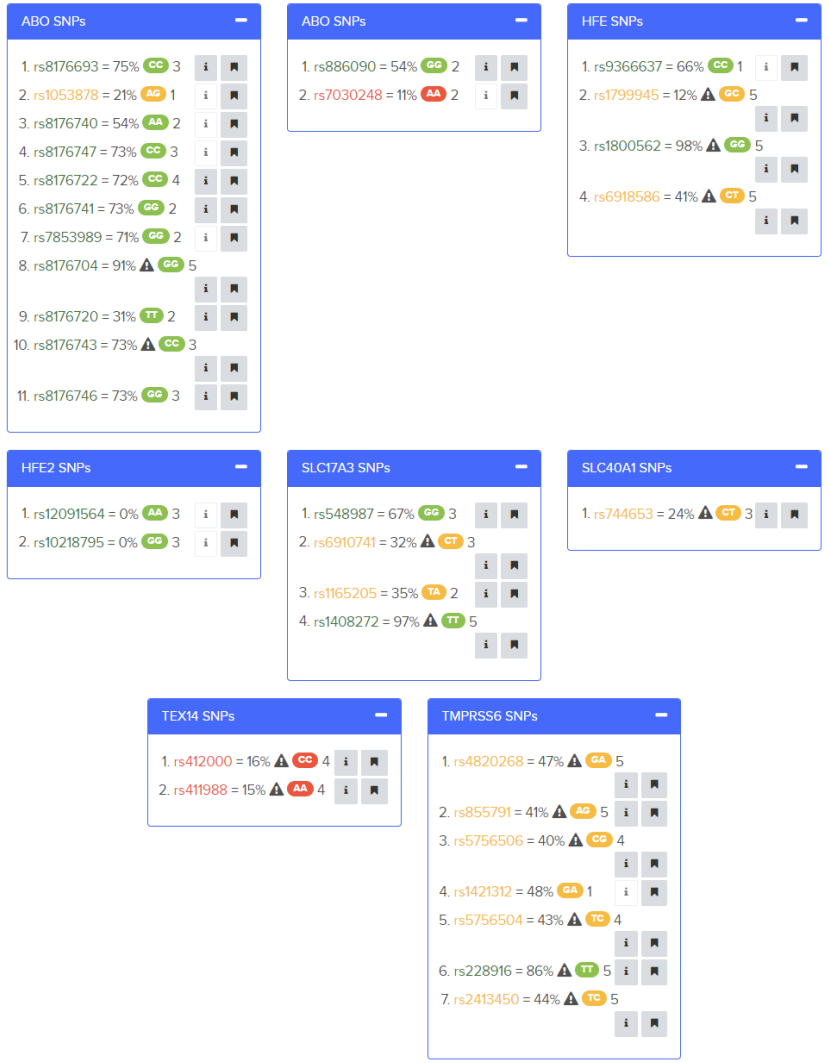
- **The VDR gene encodes the vitamin D receptor** [R]. When vitamin D binds to and activates VDR, it helps maintain the balance of minerals like calcium and phosphate in the body. VDR controls the absorption of calcium and phosphate from the gut into the bloodstream. For this reason, VDR is important for the health of bones and teeth [R]. Vitamin D and VDR also support brain health by increasing dopamine production [R]. VDR furthermore contributes to hair growth, but the mechanism of this effect is unknown [R].
- Vitamin D deficiency or a defective VDR pathway may contribute to:

Osteoporosis [R]
Cancer [R]
Diabetes [R, R]
Heart disease [R]
Neurological diseases [R]
Autoimmune diseases [R, R, R, R, R]
Infections [R]
Asthma [R]
Sun damage [R]
Kidney disease [R]
High Blood Pressure [R]
Arthritis [R]

- **rs1544410 Lower bone density and presumably less VDR activity (T).**
- **rs2228570 A= lower VDR activation**
- The presence of the A allele results in the production of a **VDR protein that is less effective as a transcriptional activator (R). Meaning the VDR protein can't induce its target genes as well.**

# Iron biomarkers

Dr. Valerio Vittone

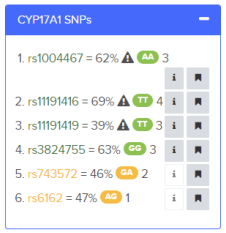



**The TMPRSS6 gene** codes for matriptase-2. Matriptase-2 is an enzyme that increases levels of iron
in the blood [R].
• Matriptase-2 increases blood levels of iron by regulating the production of hepcidin. Hepcidin is a hormone that blocks iron absorption in the gut and prevents its release from stores in the body, thereby lowering iron levels in the bloodstream [R].
• TMPRSS6 mutations have been linked to a form of iron deficiency anemia. Red blood cells require iron
to make hemoglobin, a protein that helps transport oxygen throughout the body. Low iron levels lead
to a lack of oxygen in tissues, which promotes symptoms like weakness and pale skin [R, R, R].

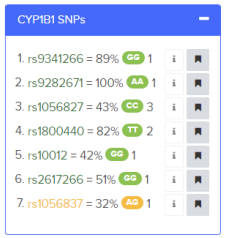
• **The SLC40A1 gene** provides instructions for making a protein called ferroportin. This protein is involved in the process of iron absorption in the body. Iron from the diet is absorbed
through the walls of the small intestine. Ferroportin then transports iron from the small intestine into the bloodstream, and the iron is carried by the blood to the tissues and organs of the body. Ferroportin also transports iron out of specialized immune system cells (called reticuloendothelial cells) that are found in the liver, spleen, and bone marrow. The amount of iron absorbed by the body
depends on the amount of iron stored and released from intestinal and reticuloendothelial cells. Research suggests that the amount of ferroportin available to transport iron out of cells is controlled by another iron regulatory protein, hepcidin. Hepcidin binds to ferroportin and causes it to be broken
down when the body's iron supplies are adequate. When the body is lacking iron, hepcidin levels drop
and more ferroportin is available to bring iron into the body and to release it from storage.
• **TEX14 The A allele of rs411988** is reported to be associated with Ferritin Measurement (R) .
**Your genotype (AA) is homozygous for this risk allele indicating decrease for Iron status**
**biomarkers (ferritin levels).**

# Estrogen metabolism including some crucial genes effecting estrogen metabolism eg MTHFR SOD2 NQ01

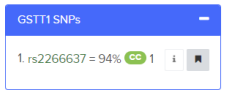
Dr. Valerio Vittone

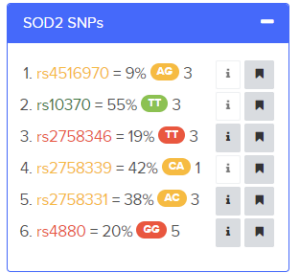












**MTHFR**

- The enzymatic activity of MTHFR in double heterozygotes for *MTHFR* C677T and A1298C polymorphisms **is lower than the activity present in each variant separately** [R]. Reduction of the MTHFR enzyme activity results in a decreased conversion of the amino acid homocysteine to methionine and **accumulation of homocysteine in the blood**. Abnormally elevated homocysteine levels are referred to as homocystinuria or hyperhomocysteinemia (Hhcy) [R]. The elevation of homocysteine levels in the blood may increase susceptibility to a series of diseases [R, R1].
- The C677T polymorphism has been linked to an increased risk of developing haemorrhagic or ischaemic stroke in different populations [R, R1, R2, R3].
- The C677T polymorphism has also been associated with ischaemic stroke in children [R].
- Individuals homozygous for the C677T polymorphism who also have low folate levels have a higher risk for developing heart disease [R].
- Polymorphisms of the *MTHFR* gene have been associated with **neuronal tube defects (NTD) such as anencephaly and spina bifida in newborns** [R].
- The *MTHFR* C677T **polymorphism is strongly associated with the development of unipolar depressive disorder, bipolar disorder** and **schizophrenia** [R, R1].
- C677T mutation is associated with the risk of **development of autism spectrum disorders** [R, R1, R2, R3].
- It has been shown that *MTHFR* mutations are linked with the development of **Alzheimers and Parkinsons disorders** [R, R1].
- The *MTHFR* polymorphisms may be linked to multiple sclerosis but the evidence is controversial [R, R1, R2].
- *MTHFR* polymorphisms confer susceptibility to migraines with or without aura [R, R1, R2].
- The C677T polymorphism **may contribute to an elevated increase of the risk for diabetes or diabetic nephropathy in patients with type II diabetes**

# Vitamin B12 Metabolism, Conversation, Transport and Absorption

Dr. Valerio Vittone

**FUT2 SNPs**

1. rs503279 = 16% CC 3
2. rs1047781 = 86% AA 5
3. rs516246 = 14% TT 5
4. rs632111 = 13% GG 5
5. rs504963 = 15% AA 5
6. rs281377 = 30% CC 3
7. rs281379 = 8% AA 3
8. rs281380 = 30% TT 3
9. rs492602 = 14% GG 5
10. rs602662 = 15% AA 3
11. rs601338 = 14% AA 3

**GIF SNPs**

1. rs35211634 = 82% TT 1

**MMAB SNPs**

1. rs7134594 = 29% TT 2
2. rs9593 = 29% TT 3

**MMADHC SNPs**

1. rs7578361 = 19% GG 2

**MTR SNPs**

1. rs1805087 = 33% GA 2
2. rs1770449 = 32% CT 1
3. rs2275565 = 39% TG 4

**MTRR SNPs**

1. rs10380 = 62% CC 1
2. rs1801394 = 41% GA 1
3. rs1532268 = 39% TC 2
4. rs1802059 = 39% AG 1
5. rs2287780 = 87% CC 1
6. rs162036 = 58% AA 1

**MUT SNPs**

1. rs9473555 = 46% GG 3
2. rs9369898 = 46% GA 4

**TCN1 SNPs**

1. rs34324219 = 10% AC 5
2. rs526934 = 32% GA 4

**TCN2 SNPs**

1. rs1801198 = 46% GC 1
2. rs2283873 = 71% GG 2

- **The MMAB gene codes for a protein, methylmalonic aciduria (cobalamin deficiency)** cblB type. Mutations are caused by the vitamin B12-dependent methylmalonic aciduria linked to the cblB complementation group [R].
- Methylmalonic acidemia At least 25 mutations in the MMAB gene have been found to cause methylmalonic acidemia, a condition characterized by feeding difficulties, developmental delay, and long-term health problems. Some of these genetic changes delete or duplicate a small amount of genetic material in the MMAB gene.
- Other mutations change a single protein building block (amino acid) used to make the MMAB enzyme. Researchers believe that nearly all of these mutations lead to the production of a nonfunctional version of the enzyme.
- As a result, AdoCbl cannot be made properly. A lack of AdoCbl impairs the function of methylmalonyl CoA mutase, which results in the incomplete breakdown of certain proteins and lipids. This defect allows toxic compounds to build up in the body's organs and tissues, causing the signs and symptoms of methylmalonic acidemia.

The MMAB gene provides instructions for making an enzyme that is involved in the formation of a compound called **adenosylcobalamin (AdoCbl).**

- **AdoCbl, which is derived from vitamin B12 (also known as cobalamin), is necessary for the normal function of another enzyme known as methylmalonyl CoA mutase. This enzyme helps break down certain proteins, fats (lipids), and cholesterol.**
- The **MMAB enzyme is active in mitochondria**, which are specialized structures inside cells that serve as energy-producing centers. Once vitamin B12 has been transported into mitochondria, the **MMAB enzyme converts a form of the vitamin called cob(I)alamin to AdoCbl**. Studies suggest that this enzyme may also deliver AdoCbl to methylmalonyl CoA mutase.

- Your MUT enzyme is working lower than average

•Your genotype (**GA**) is potentially associated with **increase for Homocysteine Measurement**

•**Supplementation with Adenosyl B12 recommended**

# HISTAMINES

Dr. Valerio Vittone

**AOC1 SNPs**

1. rs1049793 = 32% CC 1
2. rs2052129 = 66% GG 2
3. rs10156191 = 51% CC 3
4. rs1049742 = 90% CC 3
5. rs1005390 = 69% TT 3
6. rs17173637 = 90% TT 3
7. rs2071517 = 48% GG 3

**DAO SNPs**

1. rs3741775 = 34% CA 2
2. rs2070586 = 49% GG 1
3. rs4623951 = 38% CT 1

**HDC SNPs**

1. rs2073440 = 87% TT 2
2. rs16963486 = 96% AA 1

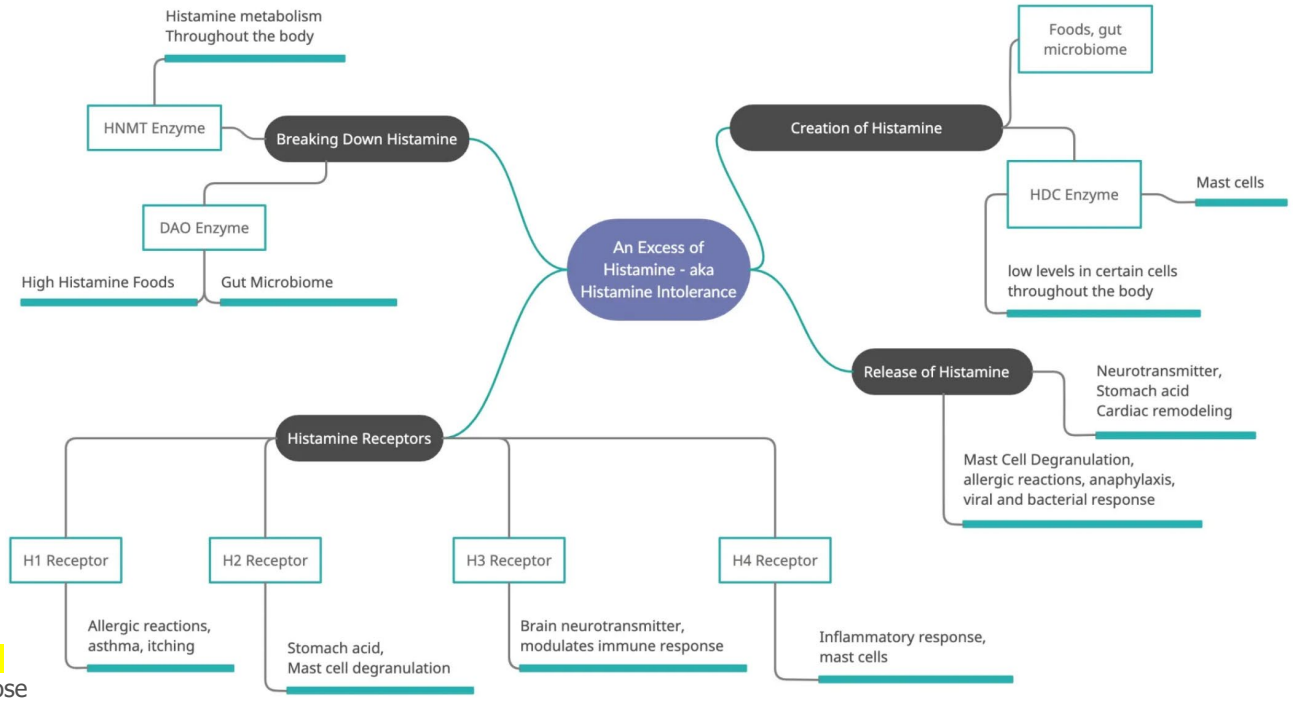
**HNMT SNPs**

1. rs1050891 = 58% AA 3

**MAOA SNPs**

1. rs979606 = 22% TT 2
2. rs6609257 = 10% AA 3
3. rs909525 = 18% TT 4
4. rs2064070 = 16% TT 2
5. rs1137070 = 16% CC 4
6. rs2072743 = 12% CC 3
7. rs3027409 = 43% TT 3
8. rs979605 = 17% GG 2
9. rs6323 = 22% TT 4

## Histamine Intolerance Mind Map

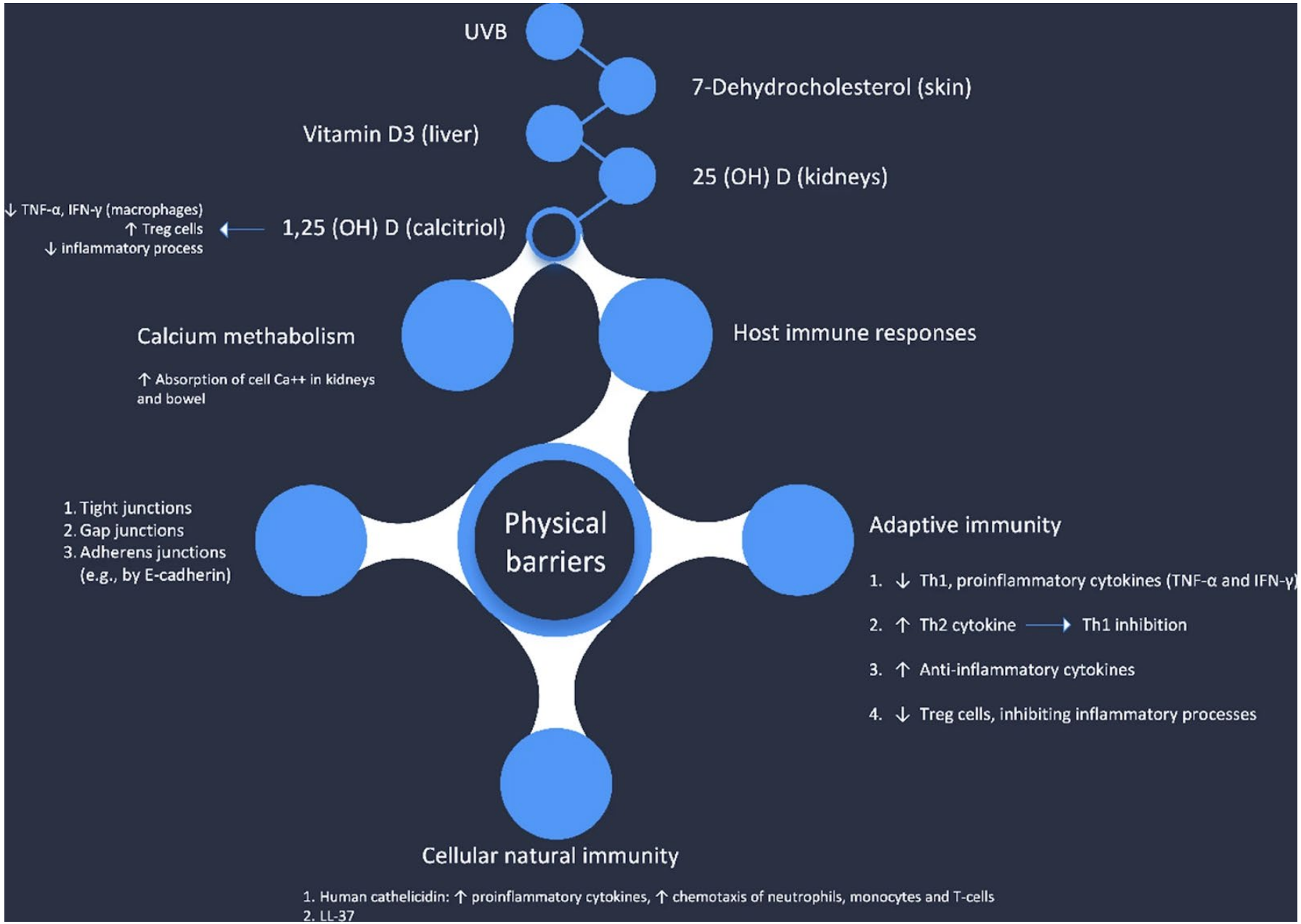



**DAO Rs3741775 The "A" allele was associated with:** reduced prepulse inhibition (PPI) and worse performance in working memory tasks and a personality pattern characterized by attenuated anxiety. Those individuals homozygous for the "A" and "C" alleles showed reduced PPI and working memory performance only in AC+ individuals with high trait anxiety [R]. Recommendation: Histamine Block Pro or normal

•**FAST MAOA LESS AVAILABLE SEROTONIN > MORE CRAVINGS DEPRESSION AND ANXIETY PAIN**

**HNMT rs1050891 The Major "A" allele is associated with:**
•"AA" indicates an increase in ADHD behavior for children when they have been exposed to certain food additives: sunset yellow, carmoisine, tartrazine, ponceau 4R, quinoline yellow, allura red AC and sodium benzoate. (R)
•It's believed that "AA" increases histamine levels and this is responsible for the ADHD behavior. (R)

•**MAOA** (Monoamine Oxidase A) is a gene responsible for the breakdown of hormones such as dopamine, serotonin, and norepinephrine in the body. [R]
**rs 2072743**
**Mechanism**:
•TT= Normal levels of Monoamine Oxidase A (MAOA) gene in the body
•T (Major allele)= Normal levels of MAOA in the body
•C (Minor allele)= Increased levels of MAOA in the body
**The Minor "C" allele is associated with**:
•Increased risk of depression and major depressive disorder (MDD) [R].
•Increased risk of experiencing migraines without Aura [R].
•Increased cancer prognosis and increased survival rates [R].
•Increased risk of cardiac cell damage during cardiac injury [R].


UVB
7-Dehydrocholesterol (skin)
Vitamin D3 (liver)
25 (OH) D (kidneys)
↓ TNF-α, IFN-γ (macrophages)
↑ Treg cells
↓ inflammatory process
1,25 (OH) D (calcitriol)
Calcium methabolism
↑ Absorption of cell Ca++ in kidneys and bowel
Host immune responses
1. Tight junctions
2. Gap junctions
3. Adherens junctions (e.g., by E-cadherin)
Physical barriers
Adaptive immunity
1. ↓ Th1, proinflammatory cytokines (TNF-α and IFN-γ)
2. ↑ Th2 cytokine → Th1 inhibition
3. ↑ Anti-inflammatory cytokines
4. ↓ Treg cells, inhibiting inflammatory processes
Cellular natural immunity
1. Human cathelicidin: ↑ proinflammatory cytokines, ↑ chemotaxis of neutrophils, monocytes and T-cells
2. LL-37