MTHFR Support & Nutrigenomics Wellness

COVID-19 Genes and SNPs

Introduction

What follows is a collection of genes and SNPs that we have found to be relevant to the current Coronavirus epidemic, COVID-19 (aka SARS-CoV-2), and their implications. This app was created by Sterling Hill of MTHFR Support in conjunction with Cynthia Smith of Nutrigenomics Wellness.

In addition to primary SNPs we have also included some secondary gene SNPs that are related to a downstream cytokine storm that may occur in some folks. The secondary genes may give further insight into individual impairment based on your individual biochemistry to sense COVID-19 virus in your body and address your individualized response to COVID-19. We have also selected relevant genes that are associated with protection of cell wall permeability and may assist with modulation of your immune system.

All of the SNPs mentioned here can be found on our new COVID-19 report available on Sterling's App.

It is important to note that neither this information nor the COVID-19 report constitutes a medical diagnosis or advice and does not replace medical advice

from your Physician. Rather, our goal is to share info that may be relevant to your personal health.

This information should not be used without the advice of a medical doctor and does not replace medical advice from your physician. We understand that many are concerned about COVID-19 and are working hard to help provide you with information regarding your genetics.

Any information provided herein regarding nutraceuticals should not take the place of medical advice from your Physician. The CDC and Physicians have advised the public to support their immune system via hand washing, etc., and both macro and micronutrients during this COVID-19 outbreak.

Like many things regarding health, genetic knowledge is one data set, that in conjunctions with other data sets and lifestyle information, that can be utilized to optimize your overall health. Genetics can enable you to identify individualize “weak links” in your health “chain”, and then address them.

When using genetic results as a data set, to optimize your health please consult an experienced Practitioner. You may find one near you on our Find a Practitioner map.

Here at MTHFR Support we are doing our best to provide you with the most up to date information as you have requested.

COVID-19

NOTE: COVID-19 and SARS-CoV-2 terms are interchangeable.

Some of the research I have cited pertains to original SAR outbreak in 2002-2003 (called SARS-CoV), but some of the same principles apply to the immune system domino effect upon SARS-CoV-2 first docking with ACE2 receptors.

COVID-19/SARS-CoV-2 in 2020 is more easily transmitted than SARS-CoV from 2002-2003, but SARS-like impacts with SARS-CoV-2 are lesser.
Having said that however, a new FURIN cleavage system in SARS-CoV-2 has made this strain more transmittable. The FURIN cleavage system was not present in coronavirus in original SARS-CoV 2002-2003 version.

I have attempted to list the enzymes/receptor proteins below in the sequential order in which they are impacted, subsequent to the docking of the COVID-19 virus onto ACE2 receptors. In some cases however, the enzymes/receptor proteins are working in parallel with the immune system.

Here is a simplified summary of the sequence of events:
Following docking of SARS-CoV-2 onto **ACE2** receptors (mostly in lungs and GI), and virus-cell membrane fusion via **TMPRSS2** and **FURIN**, a cascade of enzymatic steps and subsequent immune system mobilization occurs. Once infected, GI/lung cells are hijacked into making more viruses. The immune system reacts by stepping up its response. This response includes a robust elevation of a pro-inflammatory cytokines including **IL-1b**, early in the infection process. As described below, **NLRP3** inflammasomes, **CASP1**, **PYCARD**, and **HMGB1**, play prominent roles in this process.

SARS-CoV-2 infects alveolar endothelial cells (see, ACE2 below) and/or macrophages. Subsequently, the immune system mobilizes a response including generation of various pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF, and IFN-γ).
In some, this immune system mobilization is “overexpressed”, and can result in a severe and highly lethal respiratory disease. This severe respiratory disease is characterized by a prominent pro-inflammatory response (cytokine storm), and is referred to a bilateral pneumonia.
It should be noted that pro-inflammatory cytokines are double-edged swords that not only mobilize human immune system defense but can also drive pathologic inflammation, and therefor can play both anti-viral and pro-viral roles during a SARS-CoV-2 infection.
Postmortem data from fatal cases of the 2002-2003 SARS-CoV outbreak showed

diffuse alveolar damage including collapse and fibrous tissue in alveolar spaces, significant monocyte–macrophage infiltration, and elevated serum cytokines.
https://ajp.amjpathol.org/article/S0002-9440(10)61329-6/fulltext
It was interesting to note that during the 2002-2003 SARS-CoV, AIDS patients with deficient immune system were somewhat resistant to SARS infection, raising a possibility that an excessive immune response is attributable to the lethality of patients who die of SARS. Because death due to SARS may be the result of an overactive immune system response, scientists speculate that HIV patients' weakened immune systems may put them at a lower risk of developing the disease.
https://www.amfar.org/Will-HIV-Drugs-Help-Fight-Coronavirus/
https://khn.org/morning-breakout/dr00017448/

Primary SNPs				
SNP ID	SNP Name	Risk Allele	Your Alleles	Your Results
rs2106809	ACE2	G	AA	-/-
rs2285666	ACE2	T	CC	-/-
rs4646155	ACE2	T	CC	-/-
rs233575	ACE2	A	AA	+/+
rs879922	ACE2	G	GG	+/+
rs13306435	IL-6	A	TT	-/-
rs13447446	IL-6	T	GG	-/-
rs1474347	IL-6	A	AA	+/+
rs1524107	IL-6	T	CC	-/-
rs1554606	IL6 T22768707G	G	GG	+/+
rs1800796	IL-6	C	GG	-/-
rs1800797	IL-6	G	GG	+/+
rs2066992	IL-6	T	GG	-/-
rs2069827	IL-6	T	GG	-/-
rs2069830	IL-6	T	CC	-/-
rs2069832	IL-6	G	GG	+/+
rs2069837	IL6 A6262G	G	AA	-/-
rs2069840	IL-6	G	GG	+/+
rs2069845	IL-6	A	AA	+/+
rs2069849	IL-6	T	CC	-/-
rs2069861	IL-6	T	CC	-/-
rs10157379	NLRP3	T	TC	+/-
rs10754557	NLRP3	A	AG	+/-
rs10754558	NLRP3	C	GG	-/-
rs121908146	NLRP3	T	CC	-/-
rs12239046	NLRP3	C	TC	+/-
rs151344629	NLRP3	T	CC	-/-
rs1539019	NLRP3	C	AC	+/-
rs180177452	NLRP3	G	AA	-/-
rs180177484	NLRP3	A	GG	-/-
rs2027432	NLRP3	G	GG	+/+
rs28937896	NLRP3	C	TT	-/-
rs35829419	NLRP3	A	CC	-/-
rs3806268	NLRP3	A	AG	+/-
rs4612666	NLRP3	T	CC	-/-
rs7512998	NLRP3	T	TT	+/+
rs180177431	NLRP3	C	TT	-/-
rs3806265	NLRP3	C	TT	-/-
rs4932178	FURIN	T	CC	-/-

Primary SNPs				
SNP ID	SNP Name	Risk Allele	Your Alleles	Your Results
rs4702	FURIN	A	AG	+/-
rs17514846	FURIN	A	AC	+/-
rs2071410	FURIN	G	CC	-/-
rs12329760	TMPRSS2	T	CC	-/-
rs2070788	TMPRSS2	G	AG	+/-
rs11771443	NOS3	T	CC	-/-
rs1800779	NOS3 G6797A	A	AG	+/-
rs1800783	NOS3 A6251T	T	TA	+/-
rs1808593	NOS3	T	TG	+/-
rs2853792	NOS3	A	AA	+/+
rs3918226	NOS3	T	TC	+/-
rs3918227	NOS3	A	CC	-/-
rs4496877	NOS3	G	TG	+/-
rs743507	NOS3	T	TC	+/-
rs7830	NOS3 G10T	T	TG	+/-
rs891512	NOS3	G	AG	+/-
rs1143623	IL-1B	G	CC	-/-
rs1143627	IL-1B	A	AA	+/+
rs1143629	IL-1B	A	AA	+/+
rs1143633	IL-1B	T	TC	+/-
rs1143634	IL-1B	A	GG	-/-
rs1143642	IL-1B	G	GG	+/+
rs1143643	IL-1B	T	TC	+/-
rs16944	IL1B C-511T	G	GG	+/+
rs2853550	IL-1B	G	GG	+/+
rs3087258	IL-1B	A	GG	-/-
rs3136558	IL-1B	G	AA	-/-
rs3917356	IL-1B	T	TT	+/+
rs1045411	HMGB1	T	CC	-/-
rs1360485	HMGB1	T	TT	+/+
rs1412125	HMGB1	T	TC	+/-
rs4145277	HMGB1	C	TT	-/-
rs11618202	HMGB1	G	TT	-/-
rs1990760	IFIH1 (HLA) Ala946Thr	T	TC	+/-
rs2843710	IFNAR1	G	CC	-/-

Primary SNPs

Angiotensin-converting enzyme 2 (ACE2)

- ACE2 gene encodes the angiotensin-converting enzyme-2
- ACE2 acts as a cell surface receptor for Human coronavirus. Normally, the ACE2 receptor plays an important role in regulating the body's blood pressure and fluid balance.
- The surface expression of the ACE2 protein occurs on lung alveolar epithelial cells and enterocytes of the small intestine. As such, ACE2 is abundantly present in humans in the epithelia of the lung and small intestine.
- The coronavirus gains entry into a cell via exploiting ACE2 and type II transmembrane serine proteases (TMPRSS2) *see below*.
- Basically, the coronavirus S (spike) protein of COVID-19 binds to ACE2 with high affinity.
- Binding of the coronavirus S protein to ACE2 triggers a conformational change in the S protein of the coronavirus, allowing for proteolytic digestion by host cell proteases (TMPRSS2), thereby facilitating COVID-19 virus to human cell membrane fusions, and subsequent inflammatory immune system response (IL-6, and IL1B) *see below*.
- NOTE: Although ACE inhibitors and ARBs are useful drugs in the treatment of high blood pressure, CAD and diabetes, (used to reduce blood pressure, decrease risk of progressive kidney disease, and decrease risk of dying if one is at high cardiovascular risk), there are ongoing questions as to whether taking ACE inhibitors or ARBs increase or decrease ones susceptibility to the more severe symptoms of COVID-19.

- A March 2020 article in the Lancet, entitled, Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?, suggested that because the expression of ACE2 is substantially increased in patients with diabetes, heart disease, etc., who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs), "…*they are at higher risk for severe COVID-19 infection and, therefore, should be monitored for ACE2-modulating medications, such as ACE inhibitors or ARBs*"

- ACE2 has binding sites for Zinc and Chloride

Associated studies:
http://www.nephjc.com/news/covidace2
https://onlinelibrary.wiley.com/doi/full/10.1002/path.1570
https://www.thelancet.com/pdfs/journals/lanres/PIIS2213-2600(20)30116-8.pdf

Transmembrane protease serine 2 (TMPRSS2)

- TMPRSS2 is a Serine protease that proteolytically cleaves and activates the viral spike glycoproteins which then facilitates virus-cell membrane fusions; spike proteins are synthesized and maintained in precursor intermediate folding states and proteolysis permits the refolding and energy release required to create stable virus-cell linkages and membrane coalescence. This Serine protease facilitates human COVID-19 infection via two independent mechanisms, (1) proteolytic cleavage of ACE2, which might promote viral uptake, and (2) cleavage of coronavirus spike glycoprotein which activates the glycoprotein for cathepsin L-independent host cell entry. Essential for spread and pathogenesis of COVID-19.

- This Serine protease is expressed in type II pneumocytes in the lung (at protein level). Expressed strongly in small intestine.

- It is involved in the activation of viral glycoproteins/viral entry across a range of viruses, including SARS-CoV-2.

- NOTE: Recommended by Chinese and South Korean health authorities for the treatment of COVID-19 hydroxychloroquine and its related drug chloroquine. Hydroxychloroquine is a decades-old and inexpensive **anti-malaria drug to treat coronavirus**, and **MAY** enable faster healing times and shorter hospital stays in those who contract the infection.

    - Brand names of Hydroxychloroquine include Plaquenil, Hydroquin, Axemal (in India), Dolquine, Quensyl, Quinoric

- SARS-CoV-2 entry into cells is partially blocked in vitro by the protease inhibitor via serine protease inhibitor camostat mesylate.

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4774534/, *"…Serine protease inhibitors blocked coronavirus entry into caco-2 cells, and*

Camostat protected 6 of 10 mice from lethal infection with SARS-CoV-2."
https://en.wikipedia.org/wiki/Camostat

Associated Studies:
https://www.sciencedirect.com/science/article/pii/S0092867420302294
https://pubs.acs.org/doi/10.1021/acscentsci.0c00272
https://www.guidetopharmacology.org/coronavirus.jsp

Furin (FURIN)

- Furin is an enzyme encoded by the FURIN gene. Furin is a proprotein convertase and acts to cleave sections of inactive proteins, in order to activate them. The Furin enzyme is highly expressed in lungs.
    - NOTE: Proprotein convertases are a family of nine serine secretory proteases proteins that activate other proteins. Many proteins are inactive when they are first synthesized, because they contain chains of amino acids that block their activity. Proprotein convertases remove those chains and activate the protein.
    - The proprotein convertase family is responsible for the activation of a wide variety of precursor proteins, such as growth factors, hormones, receptors and adhesion molecules, as well as cell surface glycoproteins of infectious viruses
- In addition to processing cellular precursor proteins, Furin is also utilized by a number of pathogens. For example, the envelope proteins of viruses influenza, HIV, SARS-CoV-2 and several filoviruses including Ebola Marburg virus must be cleaved by furin or furin-like proteases to become fully functional and active.
- As previously discussed, the spikes “crowning” the SARS-CoV-2 must attach (AGT2), fuse (TMPRSS2) and gain entry to cells.
- David Veesler, senior author of the report referenced below and assistant professor of biochemistry at the UW School of Medicine, said that “*The spike is the business part as far as viral entry. It is in charge not only of attachment at the host cell surface, but also of fusing the viral and host cell membranes to allow the infection to start.*”
- He goes on to say that, “*…unlike SARS-CoV, SARS-CoV-2 includes a furin*

cleavage site at a boundary between two subunits of the spike protein. It is not yet known if this difference is expanding the kinds of cells the SARS-CoV-2 could infect or enhancing its transmissibility, in a way that might be similar to that of highly pathogenic avian flu viruses."

- https://newsroom.uw.edu/news/covid-19-coronavirus-spike-holds-infectivity-details

- Thus, when SARS-CoV-2 attaches to ACE2 cell surface receptors in the respiratory tract, it may then successfully exploit this Furin enzyme to activate its own surface glycoprotein to gain entry to respiratory tract cells. This makes SARS-CoV-2 a very easily transmittable virus. This was not the case with 2002-2003 SARS-CoV.

- Binds 3 calcium ions per subunit

- Optimum pH is 6.0

Associated Studies:
https://www.sciencedirect.com/science/article/pii/S0166354220300528
https://en.wikipedia.org/wiki/Furin

NACHT, LRR and PYD domains-containing protein 3 (NLRP3 aka CIAS1, Cryopyrin, NALP3, and Pypaf1)

- NLRP3 is a protein encoded by the NLRP3 gene.
- As the sensor component of the NLRP3 inflammasome, NLRP3 plays a crucial role in innate immunity (first line of immune defense against non-self pathogen such as SARS-CoV-2), and inflammation.
- NLRP3 regulates the secretion of pro-inflammatory cytokines interleukin 1 beta (IL-1β) and IL-18.
- In response to pathogens and other damage-associated signals, NLRP3 initiates the formation of the inflammasome polymeric complex, made of NLRP3, PYCARD see, below and CASP1, *see below*.
    - Recruitment of proCASP1 to the inflammasome promotes its activation, and CASP1-catalyzed IL1B and IL18 maturation and secretion in the extracellular milieu.
- NLRP3 activation stimuli include extracellular ATP, reactive oxygen species, K+ efflux, etc., crystals of monosodium urate or cholesterol, amyloid-beta fibers, cytosolic dsRNA, etc.
    - NOTE: Coronaviruses are positive-sense RNA viruses that generate double-stranded RNA (dsRNA) intermediates during replication, yet evade detection by host innate immune sensors. https://www.pnas.org/content/pnas/early/2017/05/02/1618310114.full.pdf
- NLRP3 activation further occurs in the presence of cytosolic dsRNA and is mediated by ATP-dependent RNA helicase (aka DHX33)

- DHX33 Independently of inflammasome activation, regulates the differentiation of T helper 2 (Th2) cells.

Associated studies:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6678949/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7025476/

- "*…melatonin has been evidenced to significantly inhibit airway inflammation, and suppress TLR3/4-mediated inflammation in liver injury. Most notably, NLRP3 is a novel molecular target for melatonin in murine model of septic response, liver injury and acute lung injury…*"

- Melatonin exhibits immunomodulatory properties.

https://www.ncbi.nlm.nih.gov/pubmed/24720799
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4163918/
https://www.ncbi.nlm.nih.gov/pubmed/15582288

- There is evidence that melatonin levels are disrupted (decreased) by electromagnetic fields such as those associated with high frequency electromagnetic fields (EMFs), particularly those associated with 4G and 5G technology.

  - Melatonin is a natural hormone produced by pineal gland activity in the brain that regulates the body's sleep-wake cycle.

  - The pineal gland is likely to sense EMFs as light but, as a consequence, may decrease the melatonin production.

  - High melatonin folks include children and women in 3rd trimester of pregnancy. Elders have lower melatonin levels.

- Melatonin peaks in early childhood (130 pg/ml)
- Melatonin begins slow decline at puberty
- 20 yrs old — 80 pg/ml
- 40 yrs old — 35 pg/ml
- 50 yrs old — 20 pg/ml
- 60 yrs old — 5 pg/ml
- 70 yrs old – negligible

https://www.ncbi.nlm.nih.gov/pubmed/23051584
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1855314/#!po=9.61538

Apoptosis-associated speck-like protein containing a CARD (PYCARD aka ASC)

- PYCARD is a protein that functions as key mediator in apoptosis (programmed cell death) and inflammation.
- The PYCARD protein is involved in macrophage pyroptosis, (a caspase-1-dependent inflammatory form of cell death) and is the major constituent of the ASC pyroptosome which forms upon potassium depletion and rapidly recruits and activates caspase-1.
    - NOTE: ASC can be either apoptosis-associated speck protein containing a CAR, or Caspase activation and recruitment domain).
    - NOTE: Pyroptosis is highly inflammatory form of programmed cell death that occurs most frequently upon infection with intracellular pathogens.
    - NOTE: Pyroptosis pyroptosis requires the function of the enzyme Caspase-1
- In innate immune response (first line of immuhne defense against non-self pathogen such as SARS-CoV-2), the PYCARD protein is believed to act as an integral adapter in the assembly of inflammasome which activates caspase-1, thereby leading to processing and secretion of pro-inflammatory cytokines.

Associated Studies:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4400844/

Caspase-1 (CASP1)

- CASP1 gene encodes the protease (enzyme) caspase-1
- CASP1 is an organosulfur-based protease that cleaves Interleukin-1 beta, thereby releasing the mature cytokines which are involved in a variety of inflammatory processes. Important for defense against pathogens.
- Upon inflammasome activation, during DNA virus infection but not RNA virus challenge, CASP1 controls antiviral immunity through the cleavage of Cyclic GMP-AMP synthase, rendering it inactive.
    - NOTE: Cyclic GMP-AMP synthase is a component of the innate immune system which detects the presence of cystolic DNA and, in response, trigger expression of inflammatory genes that can lead to cell death or to the activation of defense mechanisms.
    - DNA is normally only found in the nucleus of the cell.
    - Localization of DNA to the cytosol is associated with tumorigenesis, a viral infection or an invasion by some intracellular bacteria. The cGAS – STING pathway, including Cyclic GMP-AMP synthase, acts to detect cytosolic DNA and induce an immune response.

Associated Studies:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4163918/

Interleukin-1 beta (IL1B aka IL-1β)

- Interleukin-1 beta is a cytokine protein that is encoded by the IL1B gene
- As a caspase activation-dependent cytokine, regulated by the release of inflammasomes (NLRP3, *see above*)
- IL1B is Potent proinflammatory cytokine, and induces prostaglandin synthesis, neutrophil influx and activation, T-cell activation and cytokine production, B-cell activation and antibody production, and fibroblast proliferation and collagen production.
- The IL1B production occurs in 2 steps, each being controlled by different stimuli.
    - First, inflammatory signals, such as LPS, stimulate the synthesis and promote the accumulation of cytosolic stores of pro-IL1B (priming).
    - Second, additional signals are required for inflammasome assembly, leading to CASP1 activation, pro-IL1B processing and eventually secretion of the active cytokine. IL1B processing and secretion are temporarily associated.
- NOTE: Blocking the activity of IL-1 beta has entered the clinical arena of treating autoimmune diseases
    - https://www.ncbi.nlm.nih.gov/pubmed/15192144

Associated Studies:
https://www.uniprot.org/citations/22801494
https://www.ncbi.nlm.nih.gov/pubmed/22801494

High mobility group protein B1 (HMGB1)

- HMGB1 is a multifunctional redox sensitive protein with various roles in different cellular compartments.
- HMGB1 is also released passively by necrotic cells, and actively by macrophages/monocytes in response to exogenous and endogenous inflammatory stimuli.
- It activates macrophages/monocytes to express proinflammatory cytokines, chemokines, and adhesion molecules.
- A caspase activation-dependent cytokines, regulated by the release of inflammasomes (NLRP3, *see above*)
    - Activation of the NLRP3 inflammasome is required for HMGB1 secretion.
- The active cytokines and HMGB1 stimulate inflammatory responses. Inflammasomes can also induce pyroptosis, an inflammatory form of programmed cell death.

Associated Studies:
https://www.uniprot.org/citations/22801494
https://www.ncbi.nlm.nih.gov/pubmed/22801494

Interleukin-6 receptor subunit alpha (IL-6)

- Interleukin 6 is encoded by the IL6 gene
- IL6 is a pleotropic cytokine produced in response to tissue damage and/or infections.
- IL6 IL-6 stimulates the inflammatory and auto-immune processes in many diseases
- IL-6 is a cytokine with a wide variety of biological functions. It is a potent inducer of the acute phase response. It plays an essential role in the final differentiation of B-cells into Ig-secreting cells Involved in lymphocyte and monocyte differentiation. It acts on B-cells, T-cells, hepatocytes, hematopoietic progenitor cells and cells of the CNS. It is required for the generation of T(H)17 cells. In some cases, it also acts as an anti-inflammatory myokine. It is discharged into the bloodstream after muscle contraction and acts to increase the breakdown of fats and to improve insulin resistance. It induces myeloma and plasmacytoma growth and induces nerve cells differentiation.
- It is worth noting that, "*While several studies show the essential role of IL-6 to mount a proper immune response during some viral infections, others link this cytokine with exacerbation of viral disease. These latter findings lend support to the hypothesis that up-regulation of IL-6 during certain viral infections may promote virus survival and/or exacerbation of clinical disease.*"
- "*The clinical picture of severe acute respiratory syndrome (SARS) is characterized by an over-exuberant immune response with lung lymphomononuclear cell infiltration and proliferation that may account for tissue damage more than the direct effect of viral replication.*"

Associated Studies:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6524401/
https://www.sciencedirect.com/science/article/pii/S0168170207000470
https://www.frontiersin.org/articles/10.3389/fmicb.2019.01057/full

Nitric oxide synthase 3 [endothelial] (NOS3 aka eNOS, Constitutive NOS)

- There are three types of NOS; NOS1 (Nitric oxide synthase 1, neuronal), NOS2 (Nitric oxide synthase, inducible; aka iNOS), NOS3 (Nitric oxide synthase, endothelial; aka eNOS)
    - NOS2 enhances the synthesis of pro-inflammatory mediators such as IL6 and IL8
- NOS3 produces nitric oxide (NO) that is implicated in vascular smooth muscle relaxation through a cGMP-mediated signal transduction pathway. NO mediates vascular endothelial growth factor (VEGF)-induced angiogenesis in coronary vessels and promotes blood clotting through the activation of platelets.
- eNOS is primarily responsible for the generation of NO in the vascular endothelium, a monolayer of flat cells lining the interior surface of blood vessels, at the interface between circulating blood in the lumen and the remainder of the vessel wall. NO produced by eNOS in the vascular endothelium plays crucial roles in regulating vascular tone, cellular proliferation, leukocyte adhesion, and platelet aggregation. Therefore, a functional eNOS is essential for a healthy cardiovascular system.
- Catalytic activity:
    - 2 L-arginine + 3 NADPH + 4 O2 = 2 L-citrulline + 2 nitric oxide + 3 NADP+ + 4 H2O
- Cofactors: Heme, FAD, FMN, 5,6,7,8-tetrahydrobiopterin

Encouraging Nitric Oxide production inhibits the replication cycle of Severe

Acute Respiratory symptoms of SARS-CoV-2
"*Our results demonstrated that NO specifically inhibits the replication cycle of SARS CoV, most probably during the early steps of infection.*"

https://jvi.asm.org/content/79/3/1966

Associated Studies:
https://www.ncbi.nlm.nih.gov/pubmed/16416260
https://www.ncbi.nlm.nih.gov/pubmed/12379270
https://www.ncbi.nlm.nih.gov/pubmed/16585403

IFIH1 (HLA)

- innate immune receptor which acts as a cytoplasmic sensor of viral nucleic acids and plays a major role in sensing viral infection and in the activation of a cascade of antiviral responses including the induction of type I interferons and proinflammatory cytokines.
    - IFIH1 – Interferon-induced helicase C domain-containing protein
- The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for the current COVID-19 pandemic. An unbalanced immune response, characterized by a weak production of type I interferons (IFN-Is) and an exacerbated release of proinflammatory cytokines, contributes to the severe forms of the disease
    - Interplay between SARS-CoV-2 and the type I interferon response
- Further Resources
    - Analyses suggest that African-Americans and Chinese with low Tmaf of rs1990760 are more vulnerable to SARS-COV2 infection, apart from other genetic factors or socioeconomic conditions in these population. Taken together, an IFN-beta supplement might aid in preventing COVID-19 infection and help in development of herd immunity – PubMed

Interferon-alpha/beta receptor 1 (IFNAR1)

- Interferon-alpha/beta receptor 1 alpha chain is a protein that in humans is encoded by the IFNAR1 gene.
- IFNAR1 is a type of interferon that helps regulate the immune system.
- All type 1 interferons bind to IFN-α receptors that consist of IFNAR1 and IFNAR2 chains.
- IFNAR1 is a component of the receptor for type I interferons.
    - Genetic transfer of a functional human interferon alpha receptor into mouse cells: cloning and expression of its cDNA
    - Formation of a uniquely stable type I interferon receptor complex by interferon beta is dependent upon particular interactions between interferon beta and its receptor and independent of tyrosine phosphorylation
    - Formation of a uniquely stable type I interferon receptor complex by interferon beta is dependent upon particular interactions between interferon beta and its receptor and independent of tyrosine phosphorylation
    - Structural linkage between ligand discrimination and receptor activation by type I interferons
- A B cell auto-immune phenocopy of inborn errors of type I IFN immunity underlies life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men.

- Auto-antibodies against type I IFNs in patients with life-threatening COVID-19

Secondary SNPs				
SNP ID	SNP Name	Risk Allele	Your Alleles	Your Results
rs492602	FUT2 A12190G	G	GG	+/+
rs602662	FUT2 G12758A	A	AA	+/+
rs2855262	SOD3 489 C>T	C	TC	+/-
rs699473	SOD3	T	TC	+/-
rs1799945	HFE H63D	G	CG	+/-
rs1800562	HFE C282Y	A	GG	-/-
rs17221417	NOD2 13533C>G	G	GC	+/-
rs2066843	NOD2 19150C>T	T	TC	+/-
rs5743289	NOD2 30725C>T	T	TC	+/-
rs2066845	NOD2 Gly881Arg	C	GG	-/-
rs137852317	G6PD G477A - Class I	T	CC	-/-
rs137852336	G6PD G440A - Class I	T	CC	-/-
rs137852323	G6PD G440C - Class I	A	CC	-/-
rs137852335	G6PD V424L - Class I	G	CC	-/-
rs137852316	G6PD A423H - Class I	T	CC	-/-
rs137852321	G6PD A417H - Class I	T	CC	-/-
rs137852334	G6PD A417C - Class I	A	GG	-/-
rs137852320	G6PD L416G - Class I	C	TT	-/-
rs137852322	G6PD C415A - Class I	G	AA	-/-
rs387906468	G6PD G398L - Class I	T	CC	-/-
rs137852329	G6PD A393L - Class I	T	GG	-/-
rs137852345	G6PD A391V - Class I	A	GG	-/-
rs137852346	G6PD C299T - Class I	T	CC	-/-
rs137852319	G6PD P246L - Class I	G	AA	-/-
rs137852326	G6PD V243L - Class I	A	CC	-/-
rs1050829	G6PD A376G - Class I	C	TT	-/-
rs72554664	G6PD R493H - Class II	T	CC	-/-
rs137852324	G6PD A484H - Class II	T	CC	-/-
rs398123546	G6PD A454C - Class II	A	GG	-/-
rs137852337	G6PD A469P - Class II	T	CC	-/-
rs137852333	G6PD P383S - Class II	A	GG	-/-
rs137852327	G6PD V321M - Class II	T	CC	-/-
rs137852330	G6PD R198C - Class II	A	GG	-/-
rs5030868	G6PD S219F - Class II	A	GG	-/-
rs137852343	G6PD P203L - Class II	G	AA	-/-
rs137852331	G6PD A195A - Class II	C	TT	-/-
rs78365220	G6PD L128P - Class II	G	AA	-/-
rs137852349	G6PD T100H - Class II	G	AA	-/-
rs5030869	G6PD A365T - Class II	T	CC	-/-

Secondary SNPs				
SNP ID	SNP Name	Risk Allele	Your Alleles	Your Results
rs137852348	G6PD P511A - Class III	C	GG	-/-
rs137852344	G6PD P497A - Class III	C	GG	-/-
rs137852342	G6PD L372P - Class III	A	GG	-/-
rs74575103	G6PD A315H - Class III	T	CC	-/-
rs137852318	G6PD A312T - Class III	A	CC	-/-
rs5030872	G6PD A211V - Class III	A	TT	-/-
rs137852314	G6PD G193S - Class III	T	CC	-/-
rs137852313	G6PD G186L - Class III	T	CC	-/-
rs137852341	G6PD G161V - Class III	A	CC	-/-
rs1050828	G6PD V98M - Class III	T	CC	-/-
rs137852315	G6PD A88A - Class III	T	CC	-/-
rs78478128	G6PD A74G - Class III	C	GG	-/-
rs137852340	G6PD H62A - Class III	C	TT	-/-
rs2745557	PTGS2 A186649221G	A	AG	+/-
rs4648261	PTGS2/COX2	T	CC	-/-
rs4648298	PTGS2/COX2	C	TC	+/-
rs20417	PTGS2/COX2	C	CG	+/-
rs5277	PTGS2/COX2	G	CC	-/-
rs20415	PTGS2/COX2	T	CC	-/-
rs2066826	PTGS2/COX2	T	CC	-/-
rs689466	PTGS2/COX2	C	TT	-/-
rs4648310	PTGS2/COX2	C	TT	-/-
rs5270	PTGS2/COX2	C	GG	-/-
rs5275	PTGS2 A186649221G	A	AG	+/-
rs689462	PTGS2/COX2	G	TG	+/-
rs689465	PTGS2/COX2	C	TT	-/-
rs74315402	PRNP A117V	T	CC	-/-
rs74315406	PRNP A4680516G	G	AA	-/-
rs74315415	PRNP C4680264T	T	CC	-/-
rs74315403	PRNP D178N	A	GG	-/-
rs28933385	PRNP E200K	A	GG	-/-
rs74315405	PRNP F198S	C	TT	-/-
rs267606980	PRNP G127V	T	GG	-/-
rs74315410	PRNP G4680258T	T	GG	-/-
rs398122413	PRNP G4680499C	C	GG	-/-
rs1800014	PRNP G4680521A	A	GG	-/-
rs74315413	PRNP H187R	G	AA	-/-
rs1799990	PRNP M129V	G	AA	-/-
rs16990018	PRNP N171S	G	AA	-/-

Secondary SNPs				
SNP ID	SNP Name	Risk Allele	Your Alleles	Your Results
rs74315401	PRNP P102L	T	CC	-/-

Secondary SNPs

FUT2

This gene gives us the ability to produce an enzyme called α1,2-fucosyltransferase. When you are homozygous for any of these FUT2 SNPs on this report you only have the ability to produce 4% to 6% of this enzyme on our own. α1,2-fucosyltransferase is used to produce glycans and having trouble producing this can lead to some health issues. This enzyme is needed to help the body's natural defense system. FUT2 non secretors can have immune system impairment from diarrhea, poor beneficial gut bacteria to throat infections, ear infections and even how you respond to viruses.

Having a diet rich in oligosaccharides and polysaccharides can help vastly improve your ability to hold onto beneficial bacteria in the body. So what are some beneficial oligosaccharides and polysaccharides that and FUT2 can put in their diet to help regulate their immune system?

- Onion
- Legumes
- Wheat
- Asparagus
- Jicama
- Blueberry
- Pear
- Watermelon

- Nectarine
- Garlic
- Leeks
- Tomato
- Dandelion Root
- Bananas
- Yacon
- Chicory
- Burdock Root
- Jerusalem Artichoke
- Potato
- Grains
- Pasta
- Rice
- Bread
- Mushrooms
- Supplements containing oligosaccharides and polysaccharides

Of course when wanting to get some of these in your diet, work with your doctor to see which ones would be healthiest for you and it is always wise to eat organic and not to microwave your food.

Now does being a FUT2 non secretor help you?

Well we now know that FUT2 non secretors have more issues with bacteria and less issues with certain viruses.

So here is a little something about FUT2 showing that non secretors may have some protection against certain viruses. A few of my FB followers shared this information with me. I would encourage anyone who would like to know more about FUT2 to follow the FUT2 non secretor group on FB

Being a non-secretor seems to offer some protection against viruses. I've come across the following (caps for emphasis):

For example, NON-SECRETORS HAVE REDUCED INCIDENCE OF influenza A, influenza B, rhinovirus and respiratory syncytial virus infections,23 but increased incidence of Neisseria meningitidis, Streptococcus pneumoniae24 and Candida albicans25 infections, compared with secretors. In relation to chronic respiratory conditions, non-secretor asthma patients present with fewer exacerbations26 and non-secretor cystic fibrosis patients (with severe impairment of lung function) have prolonged time until P. aeruginosa colonisation;27 however, non-secretors with COPD have a lower FEV1%.28
https://thorax.bmj.com/…/08/thoraxjnl-2016-208775.full.pdf

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Individuals homozygous for the FUT2 NONSECRETOR GENOTYPE APPEAR TO BE RESISTANT TO INFECTION WITH NOROVIRUS9, suggesting that individuals homozygous for nonsecretor status may be unable to mediate host-microbe interactions9.
****
Also:

Severe acute respiratory syndrome (SARS) is caused by the SARS coronavirus (SARS-CoV), an RNA virus. The original SARS outbreak in the winter of 2002 to 2003 infected >8,000 individuals worldwide, with a fatality rate of 10% (292). Like other human coronaviruses, SARS-CoV infects the mucosal epithelium, causing an acute respiratory illness often accompanied by gastroenteritis. In a Hong Kong outbreak, there was an apparent association between disease transmission and ABO type (293). An epidemiology study of 34/45 hospital workers who contracted SARS after exposure to a single index patient showed that most of the infected individuals (23/34) were non-group O individuals (groups A, B, and AB). Group O individuals were relatively resistant to infection, with an OR of 0.18 (95% CI, 0.04 to 0.81; P = 0.03).

LIKE HIV, CORONAVIRUS IS AN ENVELOPED VIRUS THAT TARGETS HOST CELLS VIA A VIRAL ADHESION GLYCOPROTEIN. The SARS-CoV spike (S) protein is a 210- to 230-kDa glycoprotein with 23 potential N-glycosylation sites (292). Glycan analysis shows a wide range of structures, including complex N-glycans with 2 to 4 antennae capable of supporting ABH epitopes (292, 294). Because the virus targets respiratory and gastrointestinal mucosa, it is highly likely that most human isolates express ABH antigens on the S protein and host envelope GSLs. Like the Env protein, S protein expressing A antigen can be blocked by monoclonal anti-A and human anti-A (292).
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Nonsecretor status is associated with a decreased risk of several respiratory viral infections. By use of molecular genotyping, 2 populations of Senegalese women were examined for polymorphisms of the FUT2 gene. Among Senegalese commercial sex workers, absence of FUT2 (NONSECRETOR GENOTYPE) WAS ASSOCIATED WITH REDUCED RISK OF HUMAN IMMUNODEFICIENCY VIRUS (HIV).
****

Because various bacteria and viruses use attachment to cells as a means of causing infections, it has been determined that some NONSECRETORS have been found to have increased bacterial infections, but a DECREASED RISK IN RESPIRATORY AND GASTROINTESTINAL VIRAL INFECTIONS. Recent data from a study by Ali Suleman, et al1indicates that absence of this enzyme

resulting in a nonsecretor status is associated with a reduced likelihood of infection after exposure and a greater chance of long-term nonprogression.

SOD3

Extracellular superoxide dismutase [Cu-Zn] is an enzyme that in humans is encoded by the SOD3 gene. SOD3 is an antioxidant enzyme that catalyze the dismutation of two superoxide radicals into hydrogen peroxide and oxygen. This gene helps to protect the lungs from oxidative stress. Superoxide dismutase 3 helps to protect your DNA and cells from damage.

SOD3 is located in the extracellular matrix but it is also found in the cell junctions of airway epithelial cells and around the surface of vascular and airway smooth muscle cells (Oury et al., 1996,1994). SOD3 is involved in redox mediated signal transduction and in regulation of nitric oxide-mediated signaling across extracellular spaces (Folz and Crapo., 1994). In humans, SOD3 polymorphisms have been also associated with lung function decline and increased risk for COPD (Young et al., 2006, Wilk et al., 2007).

With the ongoing COVID-19 virus many researchers are seeing that zinc is a really important factor in the outcome of how people will recover from many types of coronaviruses. Zinc is being suggested as a nutraceutical to help protect the body from COVID-19. With this in mind, we must not offset our copper.

Foods that contain zinc:

- Cashew
- Oyster
- Lamb
- Mutton
- Hemp

- Chickpea
- Spinach
- Legume
- Whole grain
- Chocolate
- Pumpkin Seed
- Sesame
- Nuts
- Shellfish
- Cheddar cheese
- Red meat
- Shellfish
- Seeds
- Potatoes regular and sweet
- Kale
- Green Beans
- Yogurt

- Egg
- Mushrooms

Foods that contain copper:

- Liver
- Oysters
- Spirulina
- Shiitake Mushrooms
- Nuts
- Seeds
- Lobster
- Leaf vegetables
- Dark Chocolate
- Sesame Seeds
- Cashews
- Firm Tofu
- Sweet Potatoes
- Chickpeas

- Salmon
- Avocadoes

When wanting to get some of these in your diet, work with your doctor to see which ones would be healthiest for you and it is always wise to eat organic and not to microwave your food.

Hemochromatosis (HFE)

The HFE gene which is the homeostatic iron regulator provides instructions for producing a protein that is primarily located in the liver and intestines and is also found in some immune system cells. It interacts with other proteins to detect the amount of iron in the body. Some people with HFE mutations in the COVID-19 report may have trouble with their HFE organic instruction manual. When this happens there can be excessive amounts of iron in the intestines, liver and immune system cells and even other organs. This can lead to a cytokine storm.

Many who have ended up in critical care from COVID-19 are in a cytokine storm. So what can you talk to your doctor about if you are concerned about having excessive amounts of unusable iron? Getting an iron panel done including ferritin.

If you have elevated ferritin what should you avoid:

- Ascorbic acid
- Animal organ
- Elderberry syrup
- And other foods rich in iron your doctor may suggest to avoid

Types of vitamin C that are better for people with elevated ferritin:

- Ascorbate, meaning food based vitamin C vs the ascorbic form

What can your doctor suggest for lowering iron:

- Eating iron rich foods away from C rich foods Remember you must have C

in your diet which is a powerful antioxidant to fight viruses.

- A cup of dandelion root and stinging nettles has helped people with elevated ferritin remove excessive iron from the liver.
- Vitamin B1 deficiency has been related to iron overload so your doctor may want to check your vitamin B1 and adjust to your daily dosage requirement.

When wanting changes in your diet, work with your doctor to see which would be the healthiest for you and it is always wise to eat organic and not to microwave your food.

NOD2

This gene is also known as inflammatory bowel disease protein 1 gene. NOD2 gene plays a role in the immune system and recognizes bacteria and stimulates an immune reaction when working. Mutations in this gene have been related to Crohn's disease, IBD, pulmonary sarcoidosis and the way you will react to viruses. When NOD2 is working your cells use this protein to surround bacteria, viruses and other harmful invaders to destroy them. This gene has been shown to bind in response to viral RNA treatment. NOD2 acts as a pattern-recognition receptor for viruses.

Support for people with NOD2:

- Bifidobacterium
- Colostrum
- S boulardi
- B coagulins
- B subtilis
- Bone broth
- Skullcap
- Slippery elm bark
- Mullein leaf
- Prickly pear

Always talk to your medical provider before doing anything listed here.

G6PD

People who are G6PD deficient can end up with iron overload and a cytokine storm especially when given ascorbic acid. Many practitioners have discovered throughout the years it is best for G6PD deficient individuals to have food based C which is ascorbate form. As we know with an elevation of serum ferritn that those individuals are in a cytokine flare. So it is best to speak with a medical professional if you are G6PD deficient before taking any ascorbic acid supplements.

C rich foods are always safer for G6PD deficient people than ascorbic acid. Please speak with your doctor who can advise you on what C rich foods to consume during the COVID-19 outbreak. Remember that just because you have a mutation does not mean that it is always problematic.

The World Health Organization (WHO) breaks G6PD into these classifications:

- **Class I**: Severe deficiency (<10% activity) with chronic (nonspherocytic) hemolytic anemia
- **Class II**: Severe deficiency (<10% activity), with intermittent hemolysis
- **Class III**: Mild deficiency (10-60% activity), hemolysis with stressors only

PTGS2/COX2

The COX2 enzyme takes arachidonic acid and converts it into prostaglandin 2. COX2 is involved in fever, pain and antibody production. So NSAIDs known as COX2 inhibitors can reduce fever and pain when they are used. What it can also do is halt antibody production. Antibodies are made by B cells. These antibodies go out into the blood and attack viruses like COVID-19. So are NSAIDs slowing down antibody production? This could be a high risk and why reports are coming out that some of these doctors on the front lines are correlating that NSAIDs may be injuring people infected with COVID-19 more. The oldest NSAID out there is aspirin. During the 1918 Spanish flu aspirin was used at very high doses and caused toxicity and was found to kill up to 3% of those with the 1918 Spanish flu. It has been found that salicylates (COX2 inhibitors) increase lung fluid and protein levels and impair mucociliary clearance. ACE2 receptors are abundant in the kidney and that is where NSAIDs are cleared. Could this be the reason why? Could we be seeing toxicity once the ACE 2 receptors lures the virus to attach itself to the copy instead of the actual cell? So once ACE2 has COVID-19 in the kidney could this be the reason for toxicity and the reports that doctors are seeing with those on non steroidal anti inflammatories.

We will keep PTGS2/COX2 in secondary and will move it up to primary when more information becomes available. If you have any concerns because you are on daily aspirin therapy or are on other NSAIDs, please consult your physician before getting off of your medications.