A New Perspective of Genetic Associations to the Cause of Multiple Sclerosis: The Role of Genes Expressed on Chromosome 2 and 5.

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Abstract:

The literature on the causation of multiple sclerosis (MS), both genetic and environmental, extends over hundreds of years, with no firm conclusions on the exact role of autoimmunity and lifestyle. The epidemiology of MS was the basis for this review, but with a new, extensive examination of genes pertaining to each disorder, and disease of first, and second, degree relatives of those with MS. The author's motivation was to discover some relationship between MS, and notable familial conditions, as the heredity of MS is concluded to be 30%, and the disorders had a chronic and/or idiopathic nature. This investigation hoped to further understand the randomness of MS- who acquires it, and what symptoms develop- after the author's decades of observing several incidences of multiple members developing MS in a single family. Online databases for the human genome were used to link genes to MS, and symptoms, including excessive depression, fatigue and suicide rates, in coordination with linking genes for specific familial conditions including seizures, stroke, mental illness, bowel disorders, and thyroid conditions. Interesting associations were found, notably a cluster of Th2 cytokines, known to cure the animal model of MS, important receptors for neurotransmitters and hormones, a gene specific to Epstein Barr Virus, and potential genes for mitochondrial dysfunction. The results surprised the author, showing polygenic regions of chromosome 2 and 5, especially a cluster at loci 5q31-q33, may be dysregulated. The conclusion agrees with past hypotheses MS results not from a single gene, but from various genes, including those expressed in glial cells. The individual theories to the causation of MS, starting with Charcot may be explained by multiple pathways converging into a single disease outcome. In coordination with a sunlight factor, chromosome 2 appears to mediate the immune system, and inflammation, through ultraviolet radiation producing vitamin D3 in the skin, but additionally through peptides formed in the melanocyte stimulating and concentrating hormone class. The impact of stress in MS could be primary, given the loci of several stress-related and stress-modulated genes on these chromosomes, and calls for more appreciation of, and greater care for, the MS patients' state of mind.

Keywords: multiple sclerosis; MS; cause; genes; polygenic; heredity; autoimmune; diet; depression; fatigue; suicide; seizures; bowel disorders; thyroid; mitochondria; chromosome 2; chromosome 5; glial cells; sunlight; vitamin D3; ultraviolet radiation; melanocyte stimulating hormone; melanocyte concentrating hormone; stress

INTRODUCTION

Etiology

The precise etiology, and pathogenesis, of Multiple Sclerosis (MS) remain in question, centuries after the first clinical description of the condition by Jean-Martin Charcot in 1868. Charcot (1877-1889) professed a link between the symptoms of MS, and the brain's vascular supply. Leibowitz & Adler (1973) contended there was no single etiologic factor in MS, but an interaction of several. Oksenberg & Barcellos (2000) noted the genetic etiology of MS was complex one because without geography being a factor (Ulett, 1946), ethnic populations of Northern European origin had frequent MS, compared to Africans and Asians.

Theories of the cause of MS abound, and the genetic relevance has been consistent, confirmed by studies on adoption, and half-siblings (Oksenberg & Barcellos 2000). Based on repeated monozygotic twin studies, MS appears to have both genetic (30%) and environmental (70%) components, and appears to be a polygenic inheritance, with exogenous factors being the most important to triggering the condition. Poser (1994) identified genetic susceptibility as important in determining who acquires MS, however, he stressed latitude could not be ignored, as environmental agents are the triggers of symptoms of the disease. In prior publications by Dolan (2003) of a cluster study of MS, and Montesano (2012) of a review of air quality, the focus on non-inheritable environmental determinants included dietary factors prior to puberty in the prior and anthropogenic air pollution in the latter. Dolan (2003) concluded a statistical importance in protein and nutrient energy intake in development affected adult risk, and astrocytes may play a larger role in MS than was known at time of publication.

This investigation evaluates new genetic possibilities in the pathogenesis of MS, in reviewing of potential "candidate genes" at numerous chromosomal regions and loci, all leading to one condition of MS, but through multiple pathways. The regions and loci identified on chromosome 2 and 5 support Oksenberg & Barcellos (2000), who described a multifactorial etiology in MS.

The role of the stress response is reaffirmed in the manifestations of MS, as described by those who observed it in prior MS research (Goodin et al., 1999; Ackerman et al., 2002; Mohr et al., 2004). This specific review of human genes, (not congruent with rodents), on chromosomes 2 and 5 includes genes expressed in specific familial health conditions, some chronic, in the author's first, and second-degree relatives. The loci for the expression of proteins on both short (p) and long (q) arm regions, supports a hypothesis of multiple, independent genes, integrated in some manner, culminating in the disorder of MS.

Based on the number of genes pertaining to the immune system on the selected chromosomes, MS may be immune mediated, and would be capable of manifesting a range of variable symptoms among those afflicted. The pathology of MS includes edema/inflammation, patchy myelin degradation, axonal loss and neuronal death (brain atrophy), with the formation of sclerotic plaques around blood vessels, mainly venules and capillaries (Poser 1994). The result is CNS neurons are demyelinated, damaged or destroyed. Many hypothesized heterogeneous pathways for risk of MS associated with, a decrease in the average hours of sunshine to the increase in prevalence of MS (Leibowitz & Adler, 1973; van der Mei et al,. 2003), or saturated animal consumption (Swank, 2003), as well as the clumped red blood cells in the microcirculation (Swank, 1958; Courville & Courville, 1966), or a very vigorous antibody response (Poser 1994), genetic resistance based on ethnicity, and racial factors(Poser 1993), now may be substantiated. This appears to be the first hypothesis that chromosomes themselves, with neighboring genes along chromosome 2, and 5, especially 5q31 being dysfunctional regions MS is extremely unpredictable, with a different prognosis and

disease course for each individual, and may be the result of a multitude of genetic expressions isolated to chromosomes 2 and 5. Further investigations may identify integration of polymorphism, alleles, mutations, or SNPs, resulting in a neuropsychological, neuroimmunological, and neuroendocrine syndrome termed multiple sclerosis.

Pathogenesis

Many theories developed over the centuries for the observed loss of volume of white, and grey, matter in MS. Lucchinetti, Bruck, & Noseworthy, (2001) observed patterns of demyelination which were heterogeneous between patients, although homogenous in the same patient, and described a possibility different pathogenesis may operate in various groups of patients. Poser (1993) noted the extremely poor correlation between the size and location of lesions, and what presents clinically. Research experts have attributed cause of MS to vascular dysfunction (Rindfleisch, 1863), glial cells (Charcot, 1877; De Keyser et al., 1999), environmental toxins (Oppenheim, 1887; Dolan, 2003), air quality/oxygen (Montesano, 2012), heavy metal wastes (Ingalls et al., 1989; Irvine, Schiefer & Hader, 1988), latitude (Ulett, 1946; Kurtzke & Hyllested, 1979), autoimmunity (Hafler, 2014; Weiner 2004), viral infections (Kurtzke, 2000; Casetta & Granieri, 2000), chronic viral infection/pet-borne viruses(Roach, 2004), surgery (Lunny, Knopp-Sihota & Fraser, 2013), radiation (Motamed, et al., 2014), trauma (Poser & Vernant, 1993; Leibowitz & Adler 1973), oxidative damage (Haider, et al., 2016), mitochondrial dysfunction (Madsen et al, 2017; Wahls, 2010), disorder of neuropsychiatry (Sanfilipo et al., 2006), neurodegenerative brain metabolism (Behan, Chaudhuri & Roep, 2000), death of oligodendrocytes (Cudrici et al., 2006), stress (Buljevac et al., 2003; Mohr et al., 2004), sanitation(i.e. indoor plumbing, toilets and drinking water) (Leibowitz & Adler, 1973; Lowis 1990), Scandinavian/Nordic genes (Davenport, 1921; Sutherland, 1956; Ebers 1986 in Compston 1990), Vikings (Poser 1995) and Epstein-Barr virus (Buljevac et al., 2005; Levin et al.,2010).

PROPOSED RISK FACTORS

Mitochondria

Islam (2017) reviewed the interplay of mitochondrial dysfunction and oxidative stress linking to the etiology of many diseases, including neurodegenerative diseases such as Alzheimer diseases, amyotrophic lateral sclerosis, Friedreich's ataxia, Huntington's disease, multiple sclerosis, and Parkinson's diseases. Oxidative stress results from the imbalance between ROS and antioxidants to scavenge them.

There is a consistent reduction in ATP in MS (Mao & Reddy, 2010). Adamczyk, Niedzela, & Adamczyk-Sowa (2017) reviewed the mitochondrial (MT) dysfunction theory in MS, noting the lifespan of a neuron depends on large amounts of adenosine triphosphate(ATP) derived from their MT. These authors noted if antioxidant production in the MT is disturbed, there is a 30% decrease in ATP synthesis, Ca2+ is impaired, and ROS and RNS are elevated. Mahad, Lassmann, & Turnbull (2008) reviewed the role mitochondria have in ATP, but also in Ca2+ and production of ROS, noting dysfunction in MT in lesions, as well as NAWM, and GM recognized in MS, and may be the reason for axonal dysfunction. Mahad et al., (2009) stated without axonal energy, internal Ca2+ might accumulate in the axon, leading to degeneration.

Free radicals cause loss of myelin and oligodendrocytes, which affects both the neurons and the glia. The mitochondrial damage appeared to occur prior to the inflammatory processes in MS. Reactive nitgrogen species (RNC) were also reviewed, derived from nitric oxide in the neurons, endothelial, and inducible forms. ***Ectodermal-neural cortex 1 (ENC1),*** locus 5q13.3, plays a role in the oxidative stress response as a regulator of the transcription factor Nrf2 in the cytosol, as well as being involved in the regulation of neuronal process formation and in differentiation of neural crest cells. ***Mito ribosomal protein L36 (MRPL36),*** maps to 5p15.33, and is involved in the synthesis of protein within the MT, (variant locus 2p), ***NADH-ubiquinone oxidoreductase subunit 6 (NDUFS6),*** is the first enzyme in the electron-transport-chain of the MT, and deficiency is found in neurodegenerative disorders*, **NADH: Ubiquinone reductase subunit 4 (NDUFS4),*** maps to 5q13.3 as a subunit of the mitochondrial membrane in the respiratory chain of NADH dehydrogenase. Elevated NADH levels in the liver inhibit the oxidation of fatty acids. Tryptophan is involved in the synthesis of coenzyme NAD for the electron transport chain, which is also synthesized from vitamin B3 (Richard et al., 2009).

Creatine Kinase, mitochondrial-2 (sarcomeric) (CKMT2), maps to 5q11.2, and is involved with source of ATP in muscles, and elevated in patients who suffer muscle damage and necrosis. Waring, Davidoff, & Werner, R (1989) concluded that elevated creatine kinase from chronic muscle overuse, may be the contributing factor of the neuromuscular compromise of muscle endurance in post-polio syndrome (PPS.). The supplement creatine monohydrate was administered to PPS patients to help with the muscle fatigue. ***Cytochrome C oxidase, subunit VII C (COX7C)*** maps to 5q14-q15**,** as

the ending component of the mitochondrial respiratory chain catalyzing the electron transfer from reduced cytochrome c to oxygen. **Solute Carrier Family 22 (Organic Cation Transporter), Member 5 (SLC22A5)** mapped to 5q31.1, provides instruction for making OCTN2, found in cell membranes of the heart, liver, muscles, kidneys, and other tissues, where it transports carnitine into the cell.The major source of carnitine is the diet, and is needed to bring certain types of fatty acids into mitochondria to produce ATP. Fatty acids are a major source of energy for the heart and muscles, and during periods of fasting, fatty acids are an important energy source for the liver and other tissues. Inherited autosomal recessive mutation of this gene can be supplmented with oral L-carnitine. Carnitine deficiency in adulthood may show either no signs, or merely fatigability. Ruiz-Gutierrez et al., (1999) found changing liver fatty acids to mainly omega-3 lipids, may enhance the efficiency of the antioxidant system.

Coco et al., (2003) studied the role of astrocytes in releasing ATP for neurons, through an exocytosis separate from glutamate. Martino et al. (2002), suggest raised lactate in the brain could be a sign of inflammation, local ischemia, and neuronal mitochondrial dysfunction. The hypotheses of MS and heavy metal wastes (Ingalls et al., 1989; Irvine, Schiefer, & Hader, 1988) may prove valid as metals, such as mercury, which binds to the mitochondria (Stejskal & Stejskal 1999), adversely affect cellular respiration for a cell's energy. Tabbi et al., (2015), showed a protective role for SEMAX, the ACTH peptide analog, in cells experiencing metal toxicity.

Oxidative Stress

Carvalho et al., (2014) stated oxidative stress (OS) is strongly implicated in both the inflammatory, and neurodegenerative, pathology in MS. When OS occurs, cells increase their antioxidant mechanisms. Glutathione (GSH) homeostasis shows alteration in MS, GSH being the major antioxidant in the brain for detoxifying reactive oxidants (ROS). Glutathione reductase, the enzyme that catalyzes the reaction to form GSH, is the biomarker in the CSF of patients with MS (Ibitove et al., 2016).

The critical role of GSH in protecting brain cells from oxidative stress, and xenobiotic, extends to astrocytes, as high levels of GSH are present in the CNS (Giordano, White, & Costa 2011). Astrocytes are critical in the detoxification pathways, as GSH is involved in eliminating ROS and RNS. Volterra et al., (1994) found ROS affects the uptake of glutamate in astrocytes, and only two antioxidants, SOD and glutathione appeared to alleviate the effect of ROS; vitamin C was not effective as an antioxidant. Garcion et al., (1999) found the hormone 1, 25-dihydroxyvitamin D3 (1,25 D3) potentiates the expression and activity of the specific enzyme gamma-GT in GSH metabolism, after LPS exposure. Vitamin D3 did not regulate GSH peroxidase, but it enhanced the intracellular GSH pools and reduced the RNS by LPS, and concluded that gamma-GT, GSH and 1,25 D3 have a fundamental role in astrocyte detoxification pathways.

Reactive oxygen species (ROS) facilitate damage to cells, and an evaluation by Le Vine (1992), ROS were found during demyelinating episodes in MS and were hypothesized

to play a role in the actual pathogenesis. **Glutathione peroxidase 3, plasma (GPX3)** maps to 5q33.1, the enzyme in the antioxidant system that protects cells and enzymes from oxidative damage. Groen et al., (2016), addressed the impaired antioxidant system in RBCs in MS. Shukla, Jensen & Clausen, (1997) discovered glutathione peroxidase to be deficient in the altered erythrocytes (RBC) in MS**. Antioxidant 1 copper chaperone (ATOX1)** also maps with GPX3 to 5q33.1 and functions as an antioxidant. **Glutathione peroxidase putative (GPX8**) maps to 5q11.2, has a role in the metabolism and detoxification of ROS, and exists in 27 different tissues of the human body. Yoboue et al., (2017) discovered this enzyme exists in the endoplasmic reticulum of mitochondria with a role to limit peroxide accumulation, but also in Ca2+ homeostasis in the mitochondria. Selenium is a cofactor for this GPX8.

Sun exposure

Leibowitz & Adler (1973) correlated lack of sunshine, not latitude, with high rates of MS in different countries, and noted that living in "big cities" was a risk. Tall buildings, and life in, and among, those buildings prevents access to UVR, both UVA and UVB. This hypothesis of sunlight as an exogenous environmental factor shows a relationship with melanogenesis. In their Tasmanian study, van der Mei et al., (2003), reported having higher sun exposure from age 6-15, was associated with decreased risk of multiple sclerosis in adulthood, especially if the 2-3 hour per day exposure took place in the winter months. These authors considered the number of pigmented moles, and other detectable skin damage occurring from exposure to UVR, as well as skin color, all being significant in relation to MS. Less melanin density in fairer skin, determined by the non-exposed buttock area, was associated with earlier onset of disease. The more melanin density, the less skin damage. It was determined the more sun exposure in childhood through adolescence, the less risk for MS, but results showed no evidence that sun exposure 10 years before disease onset mattered. The authors hypothesized the early exposure manipulated the immune system. Outdoor workers were less likely to die with MS than indoor workers were. Lucas et al., (2011), found similar results-sun exposure and vitamin D levels may be independent in how affect the risk for demyelination. Alaluf et al., (2002), found that epidermal melanin content is significantly greater (two fold) in chronically exposed skin than it is in skin protected from UVR. These authors also noted that Europeans have the most lightly pigmented skin, and Africans and Indians are most highly pigmented.

Blood circulation and vascular issues

Blood vessels, along with neurons and glia, work to control our cognitive functions, and impairments correlate to diseases of cognition, as in MS (Takano et al., 2007 cited in Barres, 2008). Barres (2008) classified astrocytes as highly secretory cells with G-protein coupled receptors (GPCRs) expressed on their surfaces, which when activated by the binding of neurotransmitters, result in the eventual release of Ca2+ in the endoplasmic reticulum (mitochondria) of the astrocyte (Algulhon et al., 2008 as cited in Barres, 2008). These calcium waves correlate with increased microvascular blood flow.

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Neurons signal the astrocytes to elevate the Ca2+ levels, and to release signals to regulate vasodilation, with the capability to release either vasoconstrictors or vasodilators **(**Zonta et al., 2003; Metea & Newman, 2006; Gordon et al., 2007 as cited in Barres 2008**).** Guo et al., (2005) noted that estrogen acts as a vasodilator and can affect arterial relaxation, preventing excessive vasoconstriction. Wessells et al., (2003), found both brain and spinal cord melancortin receptors are involved in penile erection. ALPROSTADIL is used clinically, as a vasodilator of arteries, to rectify impotence and erectile dysfunction suffered by in males with MS.

Once erythrocytes (RBC) have clumped, blood flow is reduced, eventually leading to the dilation of the blood vessel, and further, edema in tissue and vessel hypertrophy. Stasis and abnormal blood flow can be expected to occur within the smallest veins (Simpson et al. 1987). Chronic cerebrospinal venous insufficiency (CCSVI) is the condition where veins of the brain, and spinal cord, have impaired drainage because the veins are narrowed. Dr. Zamboni (Zamboni et al., 2009) published on the contribution of CCSVI to the development of MS, and hypothesized this impaired blood flow might lead to inflammation, as CCSVI was a comorbidity of his MS patients. *Calpastatin (CAST)* maps to 5q15, and inhibits calpain of the calpain/calpastatin system. This system is involved in the membrane fusion of neural vesicle exocytosis, as well as platelet and red cell aggregation. Neural exocytosis is the membrane fusion occurring in the final step of the neuron potentiation cycle where the information is transferred across the synapse. Momeni (2011) remarked activated calpains breakdown the cellular structure of cells by degrading membranes, cytoplasm and the nucleus, and result in apoptosis, including neuronal apoptosis following spinal cord injuries and neurodegenerative diseases. Calpains are also found in muscle, as well as the mitochondria, and play a role in apoptotic and necrotic cell death (Bhat et al., 2018). Raynaud & Marcilhac (2006) implicate calpains in the pathogenesis of Alzheimer's disease.

Prineas (1970) found a broad correlation between clinical activity of multiple sclerosis and enhanced platelet stickiness. Cullen & Swank (1954) noted intravascular aggregation and adhesiveness of blood elements, and the effects on the BBB. Roizin, Abell, & Winn, (1953) commented on a "sludged blood" in MS. Bloch, (1956) identified the "sludge" (agglutination) of blood cells in human disease, including MS. Putnam (1935, 1937) detected agglutinated platelets or red blood cells in the small veins of multiple sclerosis brains, and described vessel partially occluded by organized platelet thrombi or containing agglutinated masses of platelets or disintegrating red cells. Scheinker (1943) noted agglutination in timing to lesion formation, and Scheinker (1954) noted the circulatory disturbances in MS. Fog et al. (1955) measured platelet count in the blood of MS patients during exacerbation and found tendency of low levels, which rose upon improvement in the condition. Khan et al., (1985) concluded results suggesting that increased aggregation in platelets in MS was due to some defect in platelets themselves, and not due to plasma factor. *Fatty acid hydroxylase domain containing 2 (FAXDC2)* is mapped to 5q33.1 and plays a role in the development the

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large megakaryocytes from bone marrow, responsible for producing blood thrombocytes or platelets, necessary for blood clotting (Jin et al., 2016).

Thrombin receptors are found on platelets. Vaughan et al., (1995) discovered a role for thrombin in relation to neurons and astrocytes, in regulation of gene expression, and the outgrowth of processes from both cells, in addition to stimulating proliferation of astrocytes. When the BBB in rodents breaks down from a trauma to the CNS, thrombin is produced immediately, saving primary astrocytes from dying because of environmental causes such as hypoglycemia or oxidative stress. Neurons of the hippocampus are also protected because of they express the same thrombin receptors. These authors concluded thrombin regulates the viability of both astrocytes and neurons immediately following conditions that alter the BBB. Thrombin studies connected to MS are numerous, some including *coagulation factor XII* (Parsons et al., 2017; Zilliotto et al., 2018). Dutta et al., (2018) found astrocytes, which touch the nodes of Ranvier on axons in animal models, regulate adhesion molecules that connect myelin to axons, but myelin layers detached from the axon, when the enzyme thrombin was applied. Through regulating thrombi, the astrocytes regulate the thickness of the myelin sheaths, and how wide the nodes of Ranvier are along the axons. These authors also concluded astrocytes appear to regulate the signal speeds in the brain and blocking thrombin may stabilize myelin. **Coagulation factor II receptor and Thrombin (CF2R)** maps to 5q13 as a transmembrane *GPCR* involved in regulation of thrombotic response. Thrombin is the enzyme that facilitates blood clots, and coagulation responses. It is also a stimulus for arachidonic acid (ArAc), leading to production of prostaglandins, which affect vasodilation and thromboxane, which additionally affect platelet aggregation. Coagulation and MS received a recent review by La Starza et al., (2019*). **Coagulation factor II receptor-like 2 (F2RL2)** shares the same locus and is another *GPCR,* which plays an essential role in hemostasis and thrombosis. **Coagulation factor XII** (F12) maps to 5q35.3 and is involved in normal blood clotting, fibrinolysis, and generation of vasogenic bradykinin, and angiotensin. After an injury, clots protect the body by sealing off damaged blood vessels and preventing further blood loss. Bradykinin is a stimulus to produce ArAc, like CF2R, which further leads to leukotrienes (LT), cyclooxygenase (COX). **Leukotriene C4 synthase (LTC4S***)* maps to the same locus as F12, as the enzyme involved with production of leukotrienes. LTs are synthesized from leukocytes (various white blood cells), as well as epithelial cells in the linings of blood vessels and organs. LT are responsible for secretion of cytokines, such as IL-1a and IL-2, and interferon-gamma (IFN-y). ArAc produces inflammatory LT in macrophages. LT stimulate mast cells to release histamine, causing contraction of bronchial and smooth muscle tissue, and hypersecretion of mucous glands. Luscher (1991) showed that nitric oxide (NO) derived from endothelium, known to be a vasodilator and relaxing factor, has anti-aggregatory properties, preventing vasospasm and thrombus formation in the circulation, and helps to maintain blood flow to vital organs including the heart.

Adrenoceptor alpha 1B (ADRA1B) maps to 5q33.3, activates cell division, and regulates growth and proliferation of many cells. This gene induces abnormal growth of cells (malignancy) when infected into fibroblasts and other cell lines. These receptors stimulate second messenger Ca2+ inside a cell. They are associated with asthma. Sakaue & Hoffman (1991) concluded glucocorticoids, along with testosterone and aldosterone, regulated a transcription increase in the alpha-1B receptor. Hertz, Lovett & Nedergaard (2010) classified adrenergic receptors, function and location in the CNS of rodents. Astrocytes expressed the *B1* (glycogenolysis, increased Na+, K+, ATPase activity) a1A (glutamate uptake), and a2A (glycogen). Purkayastha & Raven (2011) found evidence for a dynamic functional role for the different a-adrenergic receptors in cerebral blood flow, and the blood brain barrier (BBB).

Poser stood steadfast a compromised BBB was primary to the condition of MS. Perivascular nerves are near smooth muscle layers in the cerebral vessels, and cause vasoconstriction, which stops the BBB from breaking down during sympathetic stimulation, such as high blood pressure. Juvenile rats have a lower density and weaker constriction by sympathetic nerves in response to NE, than mature animals. Montesano (2012) discussed the cold of the extremities- hands, nose, and feet-in MS, suggesting these symptoms associate to a vasoconstrictive response, which may not be immune mediated.

Platelet-derived growth factor receptor, beta (PDGFRB) maps to 5q32, as the receptor for PDGFB and PDGFD, and plays an essential role in the regulation of embryonic development, cell proliferation, survival, differentiation, chemotaxis and migration. It is required for normal development of the cardiovascular system. Additionally, PDGFRB plays an essential role in blood vessel development by promoting proliferation, and smooth muscle cells to endothelial cells, as well as in the migration of vascular smooth muscle cells and the formation of scar tissue at vascular injury sites. PDGFRB is also the growth factor that works with the migration and recruitment of pericytes, a type of epithelial cell. Bel et al., (2010) found pericytes responsible for the integrity of the BBB, as well as capillary blood flow, and loss of dendritic spines on neurons in the brain. Further, Montagne et al., (2018) noted pericytes appear to be involved in white matter issues in the brain.

Gard et al., (1995) studied astrocytes as a paracrine regulator of oligodendroblasts, as well as survival of oligodendrocytes, through the secretion of two cytokines. The first cytokine was platelet-derived growth factor (PDGF), and the more powerful cytokine, leukemia inhibitory factor (LIF [*LIFR* locus 5p13.1]). White matter astrocytes synthesize these trophic factors to support the oligodendrocytes, which then myelinated axons in the optic nerve. These authors concluded a disruption in the relationship between astrocytes and oligodendrocytes could affect myelination, or the repair of myelin.

Pathology of the endothelium

Martino et al., (2002) noted the endothelial dysfunction in MS, and the micro-particles released from endothelial cells during disease relapses. Tsukada et al., (1989), showed cytotoxic T-cells for cerebral endothelium as a possible mechanism for the alteration of the BBB. Noseworthy et al., (2000) studying experimental allergic encephalomyelitis (EAE), reported activated CD4+ T cells specific for one or more self-antigens are believed to adhere to the luminal surface of endothelial cells in venules of the CNS, and migrate into the CNS at the time of disruption of the blood-brain barrier. Mi, Haeberle & Barres (2001) demonstrated endothelial cells induce astrocyte differentiation, as the evolution of astrocytes occurs simultaneously with the vascular system of the brain, and their end-feet help form the blood brain barrier. ***Fibroblast growth factor 1 (FGF1, ECGF)*** maps to 5q31.3 and is a modifier of endothelial cell migration and proliferation, as well as a factor for the growth of new blood vessels. FGF1 is a member of the fibroblast growth factor (FGF) family, and besides the brain, is expressed in the heart, fat and kidneys. Plumb et al., (2002) examined the tight junctions of endothelial cells in active lesions and normal-appearing white matter in MS brains. Kang et al., (2014) determined FGF signaling is required in astrocytes to maintain their non-reactive states in normal brain, and after injury. FGF signals delays the response of astrocytes and accelerates their deactivation, and deactivating the FGF receptors results in reduced scar size without affecting neurons. Garre et al., (2010) showed *FGF1* is released in spinal cord injury by spinal astrocytes, causing a reduction in gap junction communication. A gap-junction change may promote inflammation and deprive neurons of the protection that astrocytes provide in spinal cord trauma and neurodegenerative disease. Ito, Gong, & Michikawa (2013) studied *FGF1* in astrocytes undergoing oxidative stress (OS), as astrocytes increase the release of *FGF1* under OS. OS also impaired the cholesterol synthesis of astrocytes, which may contribute to membrane permeability. The *FGF1* in rodent astrocytes also enhanced apoE and HDL generation by the glia (Ito et al., 2007). Sahni & Francis (2004) showed the receptor for *FGF1*, FGFR1, in endothelial cells binds fibrinogen, and fibrinogen supports leukocytes through intracellular adhesion molecules (ICAM-1), as in atherosclerosis. Poser (1998), *An Atlas of Multiple Sclerosis*, illustrated plaques showing "perivascular fibrinogen leakage". Fibrinogen was also a noticeable factor in Montagne et al. (2018) work on pericytes and white matter. Minagar et al., (2001) reviewed endothelial microparticles released from insulted endothelial cells in MS during exacerbation and chronic injury of endothelium, and wondered what soluble factor in the blood circulation, induced the release of EMP. Their study pointed towards leukocytes (which express MC1R) participating in the exacerbation, along with astrocytes and microglia, hypothesized to be sources of inflammation at the BBB. Mapping to 5q33.3 are ***Fibroblast growth factor 18 (FGF18),*** basic FGF, which can act as a vasogenic agent disrupting the BBB (Stamatovic et al., 2008), and ***fibroblast growth factor receptor 4 (FGFR4),*** the receptor regulating several pathways, including cell proliferation, cell differentiation, cell migration, lipid metabolism, bile acid biosynthesis, **vitamin D metabolism**, glucose uptake, and phosphate homeostasis.

Edema and inflammation

Laule et al., (2004) discovered NAWM in MS has a higher water content, and lower myelin water fraction, suggesting it could be the result of diffuse edema, inflammation, demyelination, or a combination, suggesting that myelin loss is the dominant feature of pathology in NAWM. Tartaglia et al., (2002) measured choline and creatine levels in normal appearing white matter (NAWM). The choline represents membrane phospholipids, and discovered levels are higher than is normal in MS, concluding if high choline levels occurred a year before the lesion appeared visible, perhaps this indicated altered myelin chemistry.

Normal appearing gray matter (NAGM) is 80% water, and normal white matter (NAWM) 67% water. Brain edema can manifest from leaky endothelium of damaged blood vessels, ventricular obstruction, increased water in the CSF (due to higher Na+ content), and cause damage such as the progressive atrophy of the periventricular structures, enlargement of the ventricles and rapid disappearance of the myelin in affected tissue, as well as fluid accumulating in the cytoplasm of astrocytes. Behan, Chaudhuri and Roep (2002) suggest metabolically limited WM, when compromised, will retain water and swell, showing as a T2 signal on a MRI. The macrophages enter the lesion to phagocytose the swollen myelin, which looks to be an inflammatory invasion of the immune system. These authors identified a unique reduced brain metabolism in MS, suggesting plaque formation could result from failure of metabolism of myelin, and an abnormality that water would diffuse freely across myelin. What these authors found unique to MS, along with the reduced brain metabolism, was water diffusibility was reduced along the myelin but could be reversed, indicating a metabolic neurodegeneration. The conclusion was the generalized proliferation of astrocytes.

Cytotoxic edema arises from swelling of cells, especially astrocytes-caused by toxins, or hypoxia damaging the ion pump exchanging Na+/K+ into and out of the cytoplasm, where water follows, and the cells swell. One cause of this is excessive salt intake, and Sumida et al, (2018) linked high salt to autoimmunity. Klaver et al., (2013), review ion channels in demyelinated and damaged axons require increased ATP, but dysfunctional mitochondria cannot meet the requirement, and the imbalance between energy supply and demand these authors term a "virtual hypoxia", leading to axon degeneration in the WM.

Infectious agents or salt poisoning may cause inflammation. Infectious agents may enter the CNS through blood vessels of the neural tissues, or meninges and choroid plexus at the gray-white matter junction of the cerebrum and in the thalamus. The size of the pathogenic particles commonly affects the distribution of lesions, with bacteria causing a different lesion pattern than emboli from thrombosis, larger metazoan parasites or fungal hyphae. Target cell receptors for a virus may be proteins, lipids, or neurotransmitter receptors, and either infect an oligodendrocyte, an astrocyte, or a neuron. Pfefferkorn et al., (2016) found astrocytes were the main producer of IFN-B, following viral infection in the brain. Poliovirus is believed to enter the CNS through

blood circulation, causing lesions restricted to the spinal cord, brainstem and motor cortex. Some viruses infect brain endothelial cells. Demyelination associated with stripping of myelin lamellae by macrophages, may occur in viral infected oligodendrocyte, or if the infection triggers autoallergy, but no stripping has been found in MS. Scrapie, the slow progressive prion disease in sheep, has a pathology consisting of neuronal cytoplasmic vacuoles, and gliosis, but no inflammation. Similar diseases of cattle and cats occurred in Europe (carried by mites on dogs and cats), however, it is no longer believed to be associated with MS (Feldhausen, 1965).

The hypertrophic astrocytes display phagocytosis of myelin debris (Ponath et al, 2017). Sancesario & Kreutzberg, (1986) found the supplement Ginkgo biloba, helped the astrocytes expressing low levels of NADH, and concluded that Ginkgo biloba reduced oxidative enzyme activity. The zinc-dependent metalloenzyme carbonic anhydrase (CA) pumps ions, and water, between the myelin layers (Song et al., 2012). Montesano (2012) reviewed astrocytes as sources of CA, and under periods of stress production of CA is increased. The nutrients vitamin C, and cysteine, increases CA

Blood-brain barrier

Poser (1994) noted the destruction, removal, or loss of myelin was not always a follow up to edema and inflammation. Poser (1997) claimed alterations of the BBB did not repair in MS, leaving it compromised. Stamatovic et al. (2008) identified a variety of factors involved in altering BBB permeability, with prominent role for histamine, substance P, endothelin 1, and bradykinin. In addition, growth factors, basic *FGF1*, acidic FGF2, PDGF, VEGF, EGFR, and TGF-B, associate with the hyper-permeability of the BBB. The greatest breakdown of the BBB comes with primary, or secondary, inflammatory conditions of the CNS, as endothelial junctions are remodeled (Welser, Li, & Milner, 2010), and allow the increase of leukocyte traffic into the brain. Cytokines IL-1B, TNF-a, INF-y, chemokines CCL2 and CXCL8, matrix metalloproteinases (MMP2, MMP9) attract the leukocytes. The edema of stroke and brain trauma disrupts the junctions, and Poser (1994) identified trauma as a factor in MS. Transient opening of the BBB occurs during and after epileptic seizures (various seizure loci chromosome 5).

Oligodendrocyte

Bauer et al., (2007), identify "neuropoietic cytokines" with the role to control neuron, glial, and immune responses to injury and diseases. Bauer and colleagues state LIF associates with development of astrocytes from neural stem cells, and progenitor cells, that injury to the nervous system induces LIF, which possibly promotes brain repair. Endothelial express LIF mRNA. Additionally, LIF modulates the hypothalamic-pituitary-axis (HPA) response to stress, inducing depression like behaviors*. **LIF receptor alpha (LIFR),** maps to 5p13.1. Barres (2008) suggests that LIF may be a signal for astrocytes to promote the rapid wrapping of myelin by oligodendrocytes, mentioning MS as one of the most common neurological diseases. Oligodendrocytes are lost because of axonal injury or degeneration, but how axons affect the survival of oligodendrocytes remains in

question. Axons will not survive indefinitely once they lose their myelin. Barres (2008) also mentions in major depressive disorders, there appears to be massive loss of oligodendrocytes, and myelin, within the temporal lobe. Stress reduces the new generations of oligodendrocytes in the hippocampus. Oligodendrocytes express high levels of the enzyme that promotes the synthesis of 5HT (Cahoy et al., 2008 cited in Barres, 2008).

Neuregulin 2 (NRG2) maps to 5q31.2, as a growth factor in the growth and differentiation of epithelia, neuronal, glia and other type of cells. Mature oligodendrocytes cannot initiate remyelination because they are not able to undergo mitosis or migration. The precursors of oligodendrocytes (O-2A) depend on PDGF for proliferation, differentiation, and maturation (along with *FGF2*, 5q31). Rimer et al., (2004), showed the trophic factor Neuregulin-1 (NRG1, locus 8p11-21), relates to NRG2, controls myelination in the PNS by Schwann cells, and was also found essential to the myelination in the CNS (Barres, 2008). The structure of *NRG2* is like NRG1. Stefansson et al., (2002) mapped susceptibility to schizophrenia due to expression of NRG1 at synapses, and its role in expression, and activation, of neurotransmitter receptors, including glutamate. The NRG1 gene shares a locus with those for depression. Astrocytes and neurons produce NRG1, but in MS lesions, the astrocytes have greatly reduced neuregulin expression, possibly affecting remyelination (Viehover et al., 2001).

Motor neurons, and terminal Schwann cells of the PNS, express *NRG2*, and in skeletal muscle, *NRG2* is concentrated at synapses, stimulates acetylcholine receptor (AChR**)** transcription, and appears to be the protein that regulates synaptic differentiation. Temburni & Jacob (2001) identified astrocytes have low density, but functional AChR, allowing astrocytes to respond to acetylcholine (ACh), which may influence functions related to MS such as increasing attention, arousal, and short-term memory function. Nicotine binds to the nicotinic AChR, was studied in relation with Alzheimer's (Mehta et al., 2012), and smoking is well known to affect the disease course of MS (Wang et al., 2019). Lena & Changeux (1999) refer to potential effects nicotinic therapies (via the AChR receptor), may have on schizophrenia, and the role in familial frontal lobe epilepsy.

Astrocytes

Astrocytes are involved in all disease of the CNS as 50% of the resident cells in the human brain. Astrocytes swell in brain trauma and stroke, harming the brain and, demyelinating disease and epilepsy can result from mutations in their genes. By sealing the BBB, or encapsulating infections astrocytes are helpful, but by scarring they inhibit axons from regenerating (Silver & Miller 2004, cited in Barres, 2008), or by inducing unwarranted synapses cause neuropathic pain or epilepsy (Boroujerdi et al., 2008 cited in Barres, 2008).

Protocadherin 12 (PCDH12)-Protocadherin gamma subfamily C, 5 (**PCDHGC5**), the gene cluster of protocadherin, maps to 5q31.3, with a role in neural cell-to-cell communication in the brain. The family of 22 neuronal adhesion molecules at this cluster are expressed by astrocytes, as well as neurons and when both express these molecules, the creation of excitatory, and inhibitory synapses, occurs. Garrett & Weiner (2009) furthered the understanding of astrocytes promoting synapse formation (synaptogenesis) by secreting soluble factors, and y-protocadherin. Ullian et al., (2001) raised the possibility astrocytes mediate synapse elimination by phagocytosis during development, normal adulthood, and in injury.

Aquaporin 4

Ikeshima-Kataoka (2016) described the influence LPS (bacteria) has on the AQP4 on astrocytes, causing them to express more chemokines. Ikeshima-Kataoka worked on $Ca2+$ signaling in astrocyte, describing the rapid swelling of astrocytes during brain edema, and how edema triggers $Ca2+$ in astrocytes, but is reduced in rodents who are deficient in AQP4. Hypo-osmotic stress initiates $Ca2+$ spikes in astrocytes dependent upon AQP4.

Autoimmunity

Rioux & Abbas (2005) defined MS as the inheritance of "unfortunate combination of genetic sequences" and autoimmunity associated with "several sequence variants." Poser (1992, 1993) reviewed the genetic factors that vary among ethnic groups, and singled black Africans as a group who rarely developed MS, except the ones who mixed with the white population. Poser (1994) noted it imperative ethnic homogeneity of patients, and control subjects, be considered in the interpretation of prevalence and risk factor studies. Hutterites living in Canada do not develop MS, as a group, and are noted to share consanguinity.

Suzuki et al., (1969) stated the stripping of diseased myelin from the axon had never been seen in MS. Poser (1997) stated the most debated issue in MS is the immune system's role as a matter of cause, or result, as the definite mechanism involving the lymphocytes remains unknown. Wolfgram (1979) argued the preoccupation with EAE as MS limited the investigation of MS to immunology and virology, and the immune reaction was not responsible for destroying myelin but was cleaning up the debris of demyelination and the death of oligodendrocytes. Behan, Chaudri & Roep (2002), cite Dawson, (1916) and Lumsden, (1955) to identify EAE as "an intensely aggressive inflammatory disorder in which myelin loss occurs, predominantly as a bystander reaction…opposed to MS…large demyelinating plaques, conspicuous astrocyte proliferation with or without scant lymphocytic infiltration." The abnormal increase in astrocytes seen in MS is a normal response to aid widespread neuronal necrosis, as occurs in ischemia. The astrocytic scar is a meshwork of astrocytes, and processes, which is the nervous system's mechanism of repairing large defects.

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The 1960's discovery of the rodent model of an MS attack, EAE, labelled MS as autoimmune, because of the enhanced lymphocyte trafficking occurring in the brain, the CSF being clouded by leukocytes, and oligoclonal bands for antibodies (IgG). As in other diseases causing vascular permeability, some pathology in the brain and spinal cord allows for a high protein content in the CSF. **Lymphocyte Antigen (LY64)** maps to 5q12, as part of the immune system interacting with B cells, which leads to production of antibodies, and the IgG oligoclonal bands in the cerebral spinal fluid (CSF) of those with MS. **Complement C9 (C9),** maps to 5p13.1 as the final component of the complement system of the immune system, with the role to attack the membranes of bacteria, disrupting growth. Complement helps antigen/antibody IgG clear the body of pathogens. B cells are responsible for beginning the inflammatory response against microbes, and secretion of IgG.

Immune mediation

Khaibullin et al., (2017) found data to support the role of Th1 cells in the pathogenesis of brain inflammation in MS. The pathway is leukocyte infiltration, cytokines regulating the migration of T cells across the BBB, causing demyelination, and sclerotic plaques. These authors demonstrated increased levels of IL-2RA, CCL5, CCL11, MIF, IFNy, CXCL1 &10, SCF, and TRAIL in the CSF, and IL17, CCL2-4, and IL12 were activated in the serum. The production of cytokines stemmed from CD8+, Th1 cells, as well as astrocytes, and concluded Th1 cells release the IFN-y that activates astrocytes to produce chemoattractant, chemokines. **Hepatitis A virus cellular receptor 2, (TIM3)** maps to 5q33.3, as the cell surface molecule expressed on Th1 (CD4+), CD8+ cells, regulatory T cells, dendritic cells, NK cells, monocytes, macrophage activity, and inhibits Th1 mediated auto- and allo-immune responses, and promotes immunological tolerance. Hartt-Meyers et al., (2005) found TIM, on the surface of T-cells and macrophages regulates autoimmune EAE, and allergic diseases. Hastings et al., (2009) reported that *TIM3* is expressed on a subset of activated CD4+ cells (Th1) in humans, and lower levels on Th17 cells. When this receptor was antagonized to affect transcription, CD4+ T cells secreted IFNy, IL17, IL2, and IL6, but not IL10, IL4, or TNFa. The results suggest *TIM3* as a negative regulator of human T cells, regulating Th1 and Th17 cytokine secretions.**T-cell immunoglobulin and mucin domain containing 4 (TIMD4)** maps to 5q33.1, regulates T-cell proliferation, and signaling Th1 produced TNF-b, which induces vascular endothelial cells to change their surface adhesion molecules to allow phagocytic cells to bind to them. *TIMD4* enhances the engulfment of cells that have died. **Cytotoxic T-lymphocyte-associated serine esterase-3 (CTLA3)** enzyme maps to 5q11-q12. Fink et al, (1993) hypothesized *CTLA3* may be responsible for the capacity of T-cells, and NK cells, to rupture the membranes of pathogens. Ascherio, Munger, & Lunemann, (2012) determined that CD4+ Treg cells are upregulated in the peripheral blood of those with MS. **Signal transducer and activator of transcription 4 (STAT4)** maps to 2q32.2-q32.3 and increases the activity of T cell maturation into specialized Th1 cells, and is believed to be linked to RA, SLE and other autoimmune conditions.

Antigen presenting cells

Behan Chaudhuri, and Roep (2002) strongly argue no specific antigen has been identified for MS. Astrocytes and microglia can both be antigen presenting cells (APC), and in EAE, play a critical role in providing myelin antigens to T cells (Miller et al., 2007 cited in Barres 2008). However, Oberheim et al, (2009) found the rodent and human astrocytes differed, with subtypes in humans being larger, more diverse and more complex. Myer et al, (2006) concluded that reactive astrocytes in the case of brain injury have an essential role to preserve neurons, and restrict inflammation.

Koga & Kawakami (2018) identified *CAMK4* has multiple functions and regulates gene expression in a wide range of immune cells, such as those involved in MS- the T cells, and antigen-presenting cells (APC). ***Calcium-calmodulin dependent protein kinase, type IV of brain (CAMK4)*** maps to 5q21-23, the enzyme that activates a wide range of immune cells, including T-cells and antigen-presenting cells (APC). *CAMK4* plays a role in immune response, inflammation and memory consolidation. *CAMK4* regulate CD4+ memory T-cells, which are impacted by IL2, IFN-y, and IL4, and is involved in the differentiation and survival of dendritic cells. Comabella et al., (2010) suggested dendritic cells as a potential therapy for MS, given their APC ability. In the hippocampus, *CAMK4* is involved in a process that consolidates memory through long-term potentiation. An abnormal function of this enzyme was discovered in autoimmune systemic lupus erythematosus (SLE), with an involvement of IL17. Danikowski, Jayaraman, & Prabhakar, (2017) noted an elevated level of 1L17 in MS. ***Interleukin 17B (IL17B)*** maps to 5q32, a cytokine derived from T-cells, which stimulates TNF-a and IL1B in monocytes, and is primarily localized to neuronal cell bodies. Correale, Ysrraelit, & Gaitan (2011) found Vitamin D reduces the number of IL-17 secreting cells. ***Dendritic cell associated nuclear protein (DCANP1)***, maps to 5q31.1 as the gene for the expression of dendritic cells. These immune cells are potent antigen presenting cells (APC) involved in activating naïve T cells, and they initiate antigen specific immune responses. **A disintegrin and metalloproteinase domain-19 (ADAM19)** maps to 5q33.3 and is a transmembrane protein, serving as a marker for dendritic cell differentiation. *ADAM19* is an active metalloproteinase, which may be involved in normal physiological processes such as cell migration, cell adhesion, cell-cell and cell-matrix interactions, and signal transduction. *ADAM19* is proposed to play a role in pathological processes, such as cancer, inflammatory diseases, renal diseases, and Alzheimer's disease.

Th2 cytokines

Poser (1997) argued to understand the pathogenesis of MS, there had "always been the need for the intervention of some kind of cytokine." Xiao & Link (1999) proposed that microglia and astrocytes might determine the balance of Th1 (IL-2) and Th2 (IL-4) cell responses in the immune system of the brain. Microglia represent 10% of the glia, as the immune system of the CNS, but whether microglia do more harm, or help, is unknown, (Hanisch & Kettenmann, 2007, cited in Barres, 2008). Microglia rapidly

respond to the brain tissue environment, environmental toxins including injury to neural cells or non-CNS immune cells, but do not engulf myelin debris, and amyloid deposits. Microglia secrete TNF-a, which negatively affects astrocytes, as well as IL1, NO, PGE2 and SOD (Block & Hong, 2005). Ikeshima-Kataoka (2016) work with microglia suggested they could communicate, and activate, immediately with astrocytes, oligodendrocytes, and neurons, if brain damage is occurring, producing pro-inflammatory cytokines to protect neurons from damage. Microglia phagocytose, and strip synapses of spinal motor neurons, and hypoglossal motor neurons, found in the tongue. Infections with acute poliovirus involves weakness, and PNS fatigue, due to the loss of motor units. The muscle weakness of post-polio syndrome (PPS) results from denervation, and abnormal renervation of motor units. These weak muscles take a longer time to recover, which differs from the fatigue of the PNS and CNS.

Lymphocytes, believed to have a role in MS include both T and B cells of the immune system, with cytokine receptor on their surfaces. A group of Th2 cytokines, which stimulate white blood cells (WBC) to kill infections, and cancer, map to the loci 5q23-q35. These are the cytokines allowing recovery from EAE (Martino et al., 2002). *Interleukin 3 (IL3*) is a potent growth factor, supports proliferation of stem cells, and possesses neurotrophic activity, as its mRNA is found in the brain. *Interleukin 4 (IL4)* acts as an anti-inflammatory mediator between T cells and B cells after an antigen is presented. The activated T cells secrete this cytokine to promote Th2 differentiation. The *IL4/IL13* responses are involved in regulating IgE, chemokine, and mucus production at sites of allergic inflammation. Heo, Parson, & Lawrence, (1996) found lead and mercury enhanced *IL4* production by a Th2 clone (Stejskal & Stejskal 1999). *Interleukin 5 (IL5)* is involved with the growth and differentiation of B cells and eosinophils (allergies and parasites). *Interleukin 9 (IL9)* stimulates cell proliferation and prevents apoptosis; involved in asthma. *Interleukin 13 (IL13*) regulates the immune system, inhibits pro-inflammatory cytokines and chemokines. Activated Th2 cells produce *IL13*, and *IL13* is involved in stages of B cell maturation and differentiation to downregulate macrophage activity.

IgE

The antibody response for allergic rhinitis and asthma, *Immunoglobulin E concentration, serum IgE (IGES),* maps to 5q31.1. When the allergen binds to receptor bound IgE, a release of histamine, occurs, manifesting allergy. Genetically, serum IgE is a recessive trait. Leibowitz & Adler (1973) noted a person developing allergies before 15 years of age was also significant to MS, and respiratory illnesses, which would include allergies and asthma, appeared to be important to the etiology of MS. Sylwester & Poser (1979) noted an association between MS, domestic animals and household pets, perhaps implying a mild allergic reaction to animal dander. It is also possible a highly infectious coronavirus carried in these both dogs and cats, which ends up in the spinal cord via neurons and astrocytes (Sun & Perlman, 1995). Both cats and dogs had roles in divisions of the military. Cats, as in the days of the Vikings,

accompanied Naval forces on ships, and dogs were often kept as pets in campsites during wars including WWII and Vietnam, brought in to "touch and love" the soldiers described by the author of *Love, War and Polio* (Bazzett, 2008). MS developed in soldiers in all divisions of the military, as discussed in Montesano (2012). Production, and intensity, of IgE is enhanced by the response to metals, such as mercury and aluminum (Murdoch et al., 1986 cited in Stejskal & Stejskal 1999). Under increased alcohol content, the body's level of serum IgE rises, but the rise of IgE appears to generate no allergies (Gonzalez-Quintela, Vidal & Gude, 2006).

IgA

Wang et al., (2011) reviewed a selective deficiency of IgA, and its connection to increasing the risk of developing autoimmune disorders. These authors focused on GD, SLE, T1D, CD, MG and RA, which appear to develop from MHC regions, but also from non-MHC genes. *IgA inducing protein (IGIP)* maps to 5q31.3, and enhances IgA from mucosal membranes, secreted from stimulated B cells, and acts as an antimicrobial antibody. IgA is the immune response to protein antigens, and LPS on bacteria. Rojas et al., (2019), determined B cell levels are high in the CNS of those with MS, without explanation, and are also found producing IgA in the gut of the EAE model. The IgA suppressed neuroinflammation through the anti-inflammatory cytokine IL0. IgA is found to be lower in the feces of MS patients during an exacerbation.

IL-6, LIF, CNTF

Interleukin 6 signal transducer (IL6ST), maps to 5q11.2 as the signal transducer for cytokines IL6, LIF and CNTF. Bauer et al., (2007) remarked on IL6 involvement in neuronal excitability by affecting the influx of Ca2+, activating long-term potential that might give IL6 a role in learning and memory. Danikowski et al., (2017) noted an elevated level of pro-inflammatory IL-6 secreted by cytotoxic, and helper T cells in both patients with MS, and myasthenia gravis. Brunello, et al, (2000) concluded that an increase in IL6 does not harm the brain in rodents by opening the BBB; however, it may selectively activate astrocytes. Behan, Chaudhuri & Roep (2002) argued the principle cellular abnormality in MS resides in the astrocyte. Wei & Lightman (1997) linked IL6 to neurological disorders like MS and Alzheimer's, which selectively caused profuse astrogliosis in brain cells of rodents. Their study showed no infiltration of inflammatory immune cells, no effect on the neurons, however a BBB change, as result of the astrocytic end-feet. Razavi et al., (2015) suggest CNTF and LIF may offer therapy for the neurodegeneration of MS, as an upregulation of neurotrophic factors occurs in MS. LIF appears to enhance oligodendrocytes survival and inhibit their apoptosis, and suggests mutation producing loss of CNTF, increased severity of MS. CNTF stimulates myelination directly by increasing the proliferation of oligodendrocyte precursors, and their survival. Moscarello et al., (1994) determined the myelin of patients with MS is arrested at the level of the first growth spurt occurring by age 6, does not reach developmental maturity, and would be easily degraded and set up to be an antigen. Modi et al., (2013) discovered CNTF is a trophic factor for myelination and use of

acetylsalicylic acid (aspirin) increased both mRNA, and protein expression of CNTF in human astrocytes regulated by dose-, and time-dependency. These authors also demonstrated aspirin could induce CNTF from astrocytes, as healthy astrocytes produce CNTF, concluding this new property of aspirin may benefit MS, along with other demyelinating conditions**.**

IL-31

Interleukin 31 receptor A (IL31RA), maps to 5q11.2 as the receptor for IL31 found on monocytes, and is mainly expressed on mast cells and Th2 cells. It stimulates STAT1, STAT3, and STAT5, is involved with myeloid cells, mediates an IL31 induced itch, and correlates to *IL4* in allergies (Baumann et al., 2012). Zhang et al., (2008) reviewed IL31, and IL13 as part of IL6 cytokine family. IL31 regulates hematopoiesis and immune response, causing inflammatory bowel disease *(IBD*, locus 5q31), airway hypersensitivity (allergies) and dermatitis. Might this locus associate with the dysesthesia itching, which occurs, mostly at night, in MS.

Interferon

Interferons stimulate phagocytic activity of macrophages, upregulate antibody production, stimulate inflammation, as well as induce the fever associated with viral infections. Early after infection, interferons must be present in enough quantities to be able to recover from the infection. The RNA group of viruses that regulate production of interferon include paramyxovirus, causing acute respiratory disease, mumps, measles, parainfluenza, and canine distemper in dogs. All have been causative of MS. Parasites and fungi regulate the production of interferon. The bacteria in UTIs induce the production of interferon (Metz, McGuinness & Harris, 1998). ***Interferon Regulatory Factor 1 (IRF1)*** maps to 5q31.1, and has a unique "tryptophan cluster" DNA-binding region. The IRF family of transcription factors is important in regulating interferon responses to infection by virus, bacteria, and the regulation of interferon-inducible genes, and activates both innate and acquired immune response. It also activates specific target genes involved in antiviral response, such as IFN-alpha/beta, antibacterial response such as NOS2/INOS, immune response such as Il-17 (pro-inflammatory cytokine found in MS [Hafler, 2014]), implicated in differentiation and maturation of dendritic cells, and suppressing development of Treg, and response to DNA damage. *IRF1* is a tumor suppressor, stopping tumor growth, regulating the immune response to tumor cells, and its defect is associated with gastric cancer, leukemia and lung cancer

IRF1 plays an important role in the immune response affecting NK maturation and activity, macrophage synthesis of IL12, Th1 development and maturation of CD8+ cells, the cytotoxic T cells found in lesions, which can increase vascular permeability, destroy glia and lead to the apoptosis of oligodendrocytes. *IRF1* belongs to a family of genes, which includes IRF8, which has been associated with SLE. Chrabot et al., (2013) while addressing the interferon made by T cells, found STAT1 gene polymorphisms

significant in MS patients, as well as one *IRF1* gene SNP. These authors concluded genetic variants in *IRF1* and STAT1 genes in the IFN pathway were associated with MS. Fortunato et al., (2008) concluded that genetic variants in *IRF1* and STAT1 genes of the interferon pathway were associated the MS, and HCV infection. Ikeshima-Kataoka (2016) stated IL27 was found to be upregulated in MS and affected STAT1. Vandenbroek et al., (2000) reported no association between *IRF1* and multiple sclerosis in Germany, Northern Italy, Sardinia and Sweden, however, the study Horiuchi et al., (2011) identified *IRF1* as a mediator of the IFNy, signaling which leads to the apoptosis of oligodendroglia progenitor cells (OPC).

Karpuj,cited in Oksenberg & Barcellos, 2000, reported more than 20 infectious agents have been associated with the origination, or relapse, of MS, but no single pathogen has provided a clue to what causes the susceptibility to MS, or its pathogenesis. There may be no specific pathogen, but due to *IRF1* expression, it may be a generalized biological interferon need, which perhaps plays a role in MS. Injectable interferons are still used as disease modifying therapies in for MS. Zaffaroni et al., (2008) concluded IFN-b enhanced the ability of T cells to produce catecholamine, and modified the pathways of G-protein coupled receptors, B2-AR and DR, (specifically DRD2 mRNA was decreased). Consentino & Marino (2013) reviewed the dysregulation of adrenergic and dopaminergic pathways in immune cells, and glial cells, as contributing to MS.

IL-12B

IRF1 affects IL12A/B (increased with disease activity in MS [Weiner 2004]) and IL15. ***Interleukin 12B (IL12B); Natural Killer Cell Stimulatory factor-2 (NKSF2)*** maps to 5q33.3 and is a subunit of IL2, which acts on T and NK cells. This cytokine is a part of cell-mediated immunity, and is expressed by activated macrophages to induce Th1 cell development, and sustain enough memory Th1 cells for long-term protection to an intracellular pathogen and infections**.** IL2RA receptor (10p15.1) was among the MS-associated risk loci in the *Genetic Atlas of Multiple Sclerosis* (Didonna & Oksenberg, 2017), and has been shown to induce autoreactive T cell responses when no pathogens are present. Berholdt et al., (2004) hypothesize an IL12 polymorphism might predispose to immunity which attacks "self" in the case of insulin dependent diabetes mellitus (IDDM18, locus 5q31.1-q33.1), as differentiation results in a Th1 subset. Morahan et al., (2001) reviewed autoimmune Type 1 diabetes, and sought to find the susceptibility genes yet identified. These authors reported a new susceptibility locus for IDDM18 located near IL12B, concluding the variation in the allele may influence T-cell responses for IDDM18, and other autoimmune conditions.

Benesova, Vasku & Bienertova-Vasku (2018) found an association between a polymorphism of IL12B, and progression of MS in the Czech population. Makhlouf et al., (2004) recognized IL12 as being a biomarker of disease activity, because of elevated plasma monocytes when MRI showed gadolinium marked lesions. Martino et al. (2002) suggest that IL12 upregulation is an important event in disease initiation, but found more in the progressive form of MS. Esposito et al., (2010) included IL12A as a

susceptibility locus on chromosome 3p12-q13.2 for MS, and it is among the MS-associated risk loci in the *Genetic Atlas of Multiple Sclerosis* (Didonna & Oksenberg 2017).

Additionally, IL12 inhibits sunburn cell formation by reducing UVB-induced DNA damage, and helping in repair. IL12 level drop during the 3rd trimester of pregnancy, and rise postpartum; postpartum is often a time when MS flares (Elenkov, 2001).

Human leukocyte antigen II, IL-2, and IL-1A

Different human leukocyte antigen (HLA) types have been related to MS. ***Human protein RED, IK cytokine, down-regulator of HLA II (IK),*** maps to 5q31.3, as a down-regulator of HLA II (IK), which present antigens to the immune system and modulates the immune response. Loss of the HLA II means a pathogen could escape recognition by the immune system, as in some cancers, and IK could inhibit the expression of HLA II. Santoli, et al., (1986), discovered T cells activation by a mechanism that does not involve the HLA-DR or DQ antigen expression on their surface involving B cells. In addition, IL2 dependent cultured T-cells do not play a direct role in the mixed lymphocyte reaction, for when T-cells were defective in producing IL2; it was not the expression of the IL2 receptors. ***IL2 inducible T-cell kinase (ITK)*** maps to 5q33.1 as the intracellular tyrosine kinase in T cells involved in proliferation, and differentiation for Th1 cells. CNS repair appears to rely on the IL2 (T-cell growth factor) secreted by helper T-cells (Th1) triggered by the IL1 released by macrophage and microglia. *Interleukin 1 alpha (IL1A)* maps to 2q14.1 as the pro-inflammatory cytokine expressed by microglia after acute CNS injury, or systemic LPS injection, which induces A1 reactive astrocytes, as seen in MS (Liddelow & Barres, 2017). A1 reactive astrocytes normally clear both bacteria and viruses from the CNS, and have proven to be essential in the brain after a traumatic injury (Myer et al., 2006), for only astrocytes induce the death of severed neurons in CNS. Porcelli et al., (2011) found a possible link between IL-1 levels and mood disorders.

IL-7R

Interleukin-7 receptor (IL7R) maps to 5p13.2, the crucial receptor for the development of T cells. Variants of genes for both the ligand, and the receptor, are associated with MS (Gregory et al., 2007; Zuvich et al., 2010). Lee et al., (2011) have shown a connection to MS in the Japanese and Korean population. Kakhki et al., (2015) identified this non-MHC locus for susceptibility in eastern Iranian populations. Wu et al., (2016) found the IL7R C allele was associated with an increased risk of MS. Zhuang et al., (2015) looked at variants of IL7/IL7Ra to find an association with MS among the Han population in the southeastern part of China, and determined the importance of IL7, and its receptor, was their effect in the differentiations of lymphocytes.

Macrophages, monocytes and neutrophils

Colony-stimulating factor 1 receptor (CSF1R) maps to 5q32, the receptor for the cytokine, CSF1, controlling the differentiation, and function, of macrophages. Mutations are associated with myeloid malignancy-leukemia. CSF1 is released by astrocytes to signal microglia to proliferate. Shafit-Zagardo et al., (1993) found astrocytes secreted CSF1 for the growth and differentiation of monocytes. When astrocytes were exposed to IL1, or TNF, the expression of mRNA for CSF1 was upregulated, indicating that expression of CSF1 by astrocytes can be modulated by exposure to IL-1 and TNF. ***CD14 Antigen (CD14)*** maps to 5q31.3 and is expressed by monocytes and macrophages. *CD14* takes part in mediating the innate immune response to the immune challenge of bacterial lipopolysaccharide (LPS). Metz, McGuinness & Harris, (1998) identify urinary tract infection (UTI) as affecting 90% of the MS population, and is often part of an exacerbation, and neurological progression. LPS is integrated into the cell wall of gram-negative bacteria, and activates a pro-inflammatory immune response, NO and cytokine production (Backhed et al., 2001 cited in Bien et al., 2012; Taylor, 2002. ***Leukocyte cell derived chemotaxis (LECT2)****,* maps to 5q31.1 as the chemotaxin that stimulates the attraction of neutrophils in the immune system to fight infections. *LECT2* stimulates the growth of chondrocytes and osteoblasts, and a genetic polymorphism of is related to rheumatoid arthritis (RA).

PATHOGENS OF SUSPECT

Waksman & Reynolds (1984) suggested MS is a disorder of immune regulation, being predisposed to infectious agents. Poskanzer et al., (1980) the highest rate of MS in the world in the Shetland and Orkney islands, and found no association to antibody titers, or antibodies for 17 different viruses. The Orkney and Shetland islands both share in Norwegian Viking DNA, as studied by Poser. Poser (1992; 1994) believed in the acquisition of some type of multiple sclerosis trait (MST*),* resulting in a non-specific, probably viral antigenic, challenge in a genetically susceptible individual, from a viral infection or vaccine altering the immune system and increasing the permeability of the BBB.

Epstein-Barr virus

O'Gorman, Lucas, & Taylor, (2012) reviewed three environmental exposures contributing to the risk for MS- vitamin D, Epstein Barr virus (mononucleosis), and cigarette smoking. Wang et al., (2019) studied the positive association between both smoking, and passive smoking, and the susceptibility for MS. Ascherio & Munger (2007) describe an "EBV paradox" in MS, indicating EBV negative individuals have a very low risk of MS. Martyn, Cruddas & Comptson (1993) discovered infectious mononucleosis was significantly associated with developing MS*.* Glaser et al., (1995) studied the reactivation of latent herpesviruses by psychological stress, and hormones, such as glucocorticoids (cortisol). Hormones from the HPA axis, including CRH, ACTH and somatostatin, were able to reactivate EBV. ***Minor Histocompatibility protein HB1***

(HMHB1) is mapped to 5q31.3, and is only expressed in Epstein Barr Virus (EBV). This herpes virus infects resting B-lymphocytes, and represents a "latent infection", as it continuously proliferates without production of virus particles. Sugimoto et al., (2011) discovered the MSH2-MSH3 and MSH2-MSH6 mediate the DNA of EBV. *Melanocyte stimulating hormone 3 (MSH3)* maps to 5q14.1*, melanocyte stimulating hormone 2 (MSH2)* maps to 2p21-16.3 and helps fix errors that are made during DNA replication in preparation for cell division; its pseudogene at 2p15-p14*,* and *melanocyte stimulating hormone 6 (MSH6)* maps to 2p16.3.

HHV6

Yao et al., (2010) review how HHV6 infects glial cells, and conclude there may be a link to diverse pathologis as a result. Leibovitch & Jacobson (2014) refuted the compelling evidence of HHV 6 to an immune response in the CNS, giving it an indirect or direct role in MS. Challoner et al., (1995) discovered HHV-6 infected oligodendrocytes and/or microglia in MS, but not controls. Fotheringham et al, (2008) studied the dysregulation of glutamate (GLU) uptake in astrocytes infected with both the A and B forms of human herpesvirus 6 (HHV6), and persistently infected astrocytes expressed impaired GLU uptake, showing a potential for a neurological disease as a result. The genes for two receptors of glutamate occur at loci 5q33.2 (**GRIA1**) and 5q35.3 (**GRM6**). Klaver et al., (2013) identified dysregulated glutamate homeostasis as a possible pathway to elevated internal release of Ca2+ in axons.

Parasites

Correa, Paredes, & Martinez, (2016), noted the prevalence of MS is different in every continent, due to some change in geography, and environmental characteristics. Europe and North America have the highest prevalence of MS. In Latin America, MS occurs at higher prevalence in countries with the highest European immigration. Much like Australia, the natives in Latin America do not get MS. These authors conclude that the protective factors may be ultraviolet radiation (UVR), and the presence of infectious parasites. Puerto Rico has the highest prevalence of MS among the islands of Spanish Caribbean, and Latin America. The British transferred DNA from their Viking lineage to the Caribbean islands. The Vikings possibly carried the *T. Gondii* parasite, along with other parasites noted they carried, as cats were kept aboard ships to control the population of rodents.

ENVIRONMENTAL EXPOSURES

Worldwide prevalence of MS

Populations resistant to MS in Scandinavia include the Samis, who have Asian genes, and the Finnish, descended from the Mongolians, which is genetically different from the Norwegians. North American Indians who live in Canada had a lower risk for MS, until they mixed with Caucasian genes (Rosati 2001). In the United States, geographic distribution was "undoubtedly influenced by variance in genetic susceptibility in different

race and ethnic groups." Assessing US Army veterans, blacks had half the risk of whites, and risk was lower in Asians and American Indians. Those least at risk, appear to display eumelanin, and the highest correlation was with Scandinavian origin, displaying pheomelanin. In Central and South America, South American Indians, and those of African descent, had low risk compared to the Caucasians (Rosati 2001), supporting a melanin hypothesis. In the Middle East, native-born Israelis of European, or American, origin had significantly higher prevalence rates than those originating in Asia or Africa. In New Zealand, the genetic risk for MS appears related to Scottish descendants, but whites who have Maori ancestry lowered their susceptibility to the disease (Rosati, 2001). MS does exist in Japan, with no north-south gradient, and Montesano (2012) hypothesized may be associated with Japan being a chain of volcanic islands, like the Faroe Islands. The Japanese do express freckles, of which he MC1R is responsible. The Hutterite population in Canada, which does not develop MS, interestingly is noted to express (Mc Arthur et al., 1985) ***pituitary hormone deficiency, combined, 2 (CPHD2)*** which maps to 5q35.3, and involves a premature deficiency in pituitary hormones GH, TSH, LH & FSH, which normally decline with age.

Ultraviolet radiation

Vitamin D3

Adamczyk et al (2017) noted the diverse roles played by vitamin D. This hormone modulates both innate and acquired immunity, regulating the production of Th1, Th2 cytokines, and suggesting a role in governing immune and inflammatory responses. More specifically, hormonal D3 inhibits production of Th1 cytokines, Th17 differentiation, and stimulates production of *Th2 cytokines* (5q23-35) and T-reg cells, resulting in the shift in the immune response. D3 also repairs DNA, has a role in oxidative stress, membrane transport and adhesion, noting that the vitamin D receptor (VDR) is expressed on immune cells, as well as cells within the CNS.

Melanocyte stimulating hormone

Taylor & Streilein (1996) found the CSF contains immunosuppressive neuropeptides a-MSH and VIP. Pawelek & Osber (1991) speculated MSH receptors might belong to B-adrenergic class of receptors, as MSH stimulates cyclic AMP (cAMP) production in melanoma cells. Their observations suggested the primary effect of UVR upon mammalian skin was to stimulate MSH, increasing melanin production, as well as stimulating the receptors in the CNS, including on astrocytes (MC4R). Catecholamine acting at B1-adrenergic receptors (10q24-26), increases cAMP in astrocytes, as well as, prostaglandin E_1 (PGE1), vasoactive intestinal polypeptide (VIP), α-melanocyte-stimulating hormone (a-MSH), and adrenocorticotropin (ACTH) (Evans et al., 1984). Both ACTH and a-MSH share the peptide sequence-His-Phe-Arg-Trp-which is essential for formation of melanin. The Russian produced analog of ACTH, SEMAX, is distributed as a neurotrophin, and nerve growth factor, in conditions of ischemia, stroke, and ADD (Retrieved from National Center for Biotechnology Information. PubChem Database. Semax, https://pubchem.ncbi.nlm.nih.gov/compound/122178).

Caruso et al., (2007) determined that *a-MSH* decreases iNOS and COX2 expression, and the release of NO and PGE.

Pollution

Montesano (2013) hypothesized a role of pollution in MS, based, in part, on work by Block & Calderon-Garciduehas (2009) proving air pollution is a chronic source of neuroinflammation, ROS, and linking pollution to stroke, Parkinson's and Alzheimer's. Both activated microglia cells, and pollution, appeared to change the BBB.

Carbon dioxide

Dolan (2003) concluded the possibility astrocyte were the dysfunctional glial cells in MS because Funata et al., (1982) showed swelling astrocytes brought about a lamellar separation of the myelin sheath, predominantly in the deep cerebral white matter from cyanide or carbon monoxide (CO) poisoning. Sungho & Sang-Cheon (2015) confirm the pathophysiology of CO poisoning includes WM demyelination, diffuse brain atrophy, and brain lesions in inflammation of the periventricular region, and matter in Parkinson's disorder(Li, Chou, & Lai, 2018).

Similar to the pathology of MS, in acute CO poisoning (cigarette smoking puts CO in circulation), the vascular endothelium releases NO, and platelets may release ROS, which leads to mitochondrial dysfunction, capillary leakage, leukocyte sequestration, and apoptosis. DA levels increase during the hypoxia, and excess levels last for several weeks in deep WM, causing a "delayed neurologic sequelae", further generating ROS and triggering an abnormal inflammatory response. Injury to neurons occurs, including 5HT neurons, and secondary myelin damage, which may lead to leukoencephalopathy, in which toxins target myelin, axons, oligodendrocytes, astrocytes and blood vessels in WM. In CO poisoning, in addition to anti-inflammatory steroids, hyperbaric oxygen, as well as N-acetyl cysteine (NAC), are feasible treatments (Bavarsad-Shahripour, Harrigan & Alexandrov (2014) cited in Sungho & Sang-Cheon, 2015).

Particulate matter 2.5

Kulas et al., (2018) studied for long-term effects of inflammation and neurodegeneration of particulate matter (PM2.5) in the blood circulation for a fetus. These exposed animal models, showed significantly high COX-2 in adulthood, but also increased GFAP of activated, reactive astrocytes of the temporal cortex, as well as adjusted inflammatory cytokines (IL1a, IL2, *IL4*, IL6, IL10, IFNy, *GM-CSF*, TNF-a) in the brain, and lymphoid organs, inhibiting the immune system. Genes for hematopoietic growth factors, *IL3, IL5 & GM-CSF* are mapped to the locus 5q23-31; *IL4* is mapped to 5q23.3-31.2. All 4 cytokines are within 500 kb of each other. Shi et al., (2006) reviewed *GM-CSF* as a growth factor, and immune modulator, strongly affecting functional activities of various circulating leukocytes. T cells, macrophages, endothelial cells and fibroblasts all produce *GM-CSF* when stimulated, and it acts locally to enhance host defense by recruiting circulating neutrophils, monocytes and lymphocytes.

The BDNF pathway was altered by PM2.5 in the placenta, and astrocytes were compromised during development. Kulas et al., (2018) concluded in utero exposure to PM2.5 shows toxic, long-term consequences in the brain and immune system, inflammation, behavioral alterations (memory), and broad changes in levels of cytokines. PM2.5, noted in *Clues to the Cause, Questions for a Cure* (Montesano, 2010) could originate from industrial sources. Perkovic et al., (2010) identified high-risk industrialized areas for MS in Hungary, and Bohemia, to be associated with environmental pollution, and areas of high upper respiratory viral infections. These authors note all the MS patients in the investigated area belong to a Croatian ethnic group, but their genetic German roots stemmed from areas of Saxony and Turingji (also high in prevalence). One Germanic phenotype is paler skin, often blonde, red or brown hair, and light eyes.

Li, et al., (2018) investigated how long exposure to PM2.5 promotes neuroinflammation and dysfunction at the synapses of the brain, as PM2.5 elevates COX-2 in the neurons of the hippocampus, leading to disruption of the synapses and neurological damage. The supplmenet N-acetyl-L-cysteine (NAC) suppressed COX-2, which also is associated with schizophrenia (5q11.2-13.3).

Smoking

Smoking becomes addictive as nicotine binds to nicotinic ACh receptors, and increases dopamine (DA) levels in brain. *GM-CSF* (5q31) is a cytokine in normal pregnancy, as *GM-CSF* regulates dendritic cells in the uterus, which arrange the tolerance of the fetus early in pregnancy (Moldenhauer et al., (2010). Fu et al., (2012) found cigarette smoke extract increased the expression of *GM-CSF* during pregnancy, under influence of signaling by endothelium growth factor (*EGFR,* 5q31*). GM-CSF* is essential for MHC class II, and class I mediated responses to antigens presented from the fetus, and a deficiency in *GM-CSF*, dysregulates dendritic cells, T cell tolerance, causing infertility, miscarriage and preeclampsia.

Nitric oxide

Smoking produces nitric oxide (NO), which can constrict the airways and the blood vessels. Pacher et al., (2007) reviewed the harmful oxidation form of NO, found in stroke, myocardial infarction, chronic heart failure, diabetes, chronic inflammatory disease, cancer and neurodegenerative disorder. Caruso et al., (2013) noting the expression of inducible NO synthase (iNOS) that note astrocytes and microglia are producers of high amounts of NO, when affected either by LPS, or pro-inflammatory cytokines in the brain. Elevated iNOS has been found in MS (Bo et al., 1994). Smith & Lassman (2002) concluded RNS are found at higher than normal levels in MS lesions. NO has the potential to affect the permeability of the BBB, injure oligodendrocytes, impact demyelination and axonal degeneration, and axonal conduction, but inhibiting immunomodulatory iNOS in EAE showed no results.

Research from the University of Southampton (2014) showed sunlight alters the levels of nitric oxide (NO) in the skin and blood, leading to reduced blood pressure, as UVA exposure alters NO stored in the skin, dilating the blood vessels. Blood pressure, and cardiovascular disease, follow a similar pattern to MS- they vary according to season, with higher levels observed in the winter, and in countries farther from the equator.

Heat stress

Behan, Chaudhuri & Roep (2002) discuss the finding of heat shock protein in the brains of neurological disease, such as MS. ***Heat shock protein family A (HSP70) member 4 (HSPA4)*** maps to 5q31, and links to disease, including ischemia and transient cerebral ischemia. *HSPA4* has a role in the pathway for cellular responses to heat stress. When exposed to elevated temperature, and other stimuli which impair a cell function with misfolded proteins, (e.g. hypoxia, ROS), there is a "heat shock response" (HSR) to protect the cells. Yang & Dunn (2015) performed the first study showing reduced microvascular hemoglobin saturation in the brains of those with MS, significant in relation to clinical disability, and supported the theory of hypoxic regions in the MS brain. The HSR is considered an evolutionary event to allow cells to recover from protein damage induced by stress. Bigazzi (1996) provided evidence that heavy metals induced heat-shock proteins.

Stress and its response

The stress response is not always traumatic (Mohr et al., 2004), but produces the same hormonal pathways. Stress includes worry, fear, pain, x-rays, any change to atmospheric pressure (Seyle, 1984), crowding (cities), noise (auditory stress), group housing, and unexpected events. The intensity of the biological response is based on individual adaptability and coping ability. Seyle also determined the liver is the central chemical lab and performs three tasks in the biochemical response to stress-produces energy, checks for excessive corticoids, and detoxifies environmental pollutants and poisons. If the stressors are simultaneous, and inescapable, such as a move, full-time work, care of children/mate and household, after many months can lead to exhaustion called burnout. Walsh & De Chello (2001) studied the excess of death from autoimmune conditions in teachers. Sternberg, 2001; reflects both nurses and teacher have the risk of burnout,as both professions offer care-giving, and besides psychological burnout, a physiological burnout manifests with a flattened cortisol response, and inability to respond to any stress with even the slightest burst of cortisol. Chronic, unrelenting stress can change the stress response itself, and the hormonal system, too. Depression is the stress response stuck on "on'.

Gold et al., (2010) found smaller volume in the hippocampus of those with MS, and concluded that smaller CA23DG sub-regional volumes were associated with hypersecretion of cortisol, and depression in MS. Cortisol is also associated with the circadian rhythm of the body, as circadian cues, stress, and emotional depression

stimulates the HPA axis, resulting in bound and unbound cortisol (Bhagavan & Ha, 2015).

The stress response generates NE, EPI (beta-2, alpha-1), ACTH (*POMC*), STH, and MSH (*POMC*) (Borysenko & Borysenko, 1982). Montero-Melendez (2015) comments on the forgotten role that ACTH has as a therapy, which will not increase cortisol, as it acts as an anti-inflammatory therapy.

Chronic stress reduces circulating T-cells. STH is needed to recover the immune function following stress and influences the sodium/potassium balance in the body, as does y-MSH binding to MC3R, and regulating the amount of sodium in the body, controlling blood pressure. One of the 3 melantropins from cleavage of POMC is B-lipotropin (B-LPH), works on the steroid aldosterone, which stimulates the absorption of sodium by the kidney, and maintains the balance between water and salt (Pawelek & Osber, 1991). Liberzon et al., (2014) discovered EPI and NE function was altered by childhood trauma, and through a polymorphism of the ADRB2 gene (5q32), is linked to adult PTSD, or other psychiatric disorders, such as chronic pain. Jacob et al., (2017) discovered at a certain time of year, starches and carbohydrates, brought about a higher ACTH level in adult and aged horses

Glucocorticoid receptor and resistance

In the stress response, the corticosteroids inhibit immunity far greater than NE or EPI, but both reduce mature T-cells, depending on the type of stress, chronicity of it, and the control of the organism. A chronically stressed individual is more susceptible to polio and cold sores. **Glucocorticoid Receptor (GRL)** maps to 5q31 and is expressed in the hippocampus of the brain. In rodent studies, the methylation of this gene was reduced by "poor parenting (mothering)" of pups, resulting in the pups producing higher levels of stress hormones for life (Weaver et al., 2004). This receptor plays a role in anti-inflammatory responses, including the Muller astrocytes in the retina of the eye (Galina et al., 2014). In *Atlas of Multiple Sclerosis* (Poser, 1998*),* Figure 13, indicates leakage from the blood vessel walls in the retina (Lightman et al., 1987), noting abnormal endothelial tight junctions in the myelin-free structure of the retina. **Glucocorticoid receptor deficiency, cortisol resistance (GCCR)** maps to 5q31.3, and a mutation to 5q31. Mohr et al., (2004) noted in animal models, sustained cortisol reduces the number and capacity of receptors for cortisol on immune cells, thus the susceptibility to illness because of stress. Chrousos et al., (1983) reported patients with a less severe resistance to cortisol show nothing clinically, and only upon examination is the dysfunction in the metabolism of cortisol discovered.

Prostaglandin E2

Some vasoactive compounds include NO, adenosine, and pH, but the primary mechanism for astrocytes to mediate the dilation of blood vessels is the release of prostaglandin E2 (PGE2), which is COX-1 dependent. Astrocytes increase cytosolic Ca2+ release by the application of neurotransmitters, simultaneously there is an

increase in PGE2, increased microvascular blood flow, and this control of excess blood flow, controls the supply of oxygen to the brain. **Prostaglandin E receptor 4 (PTGER4)** is a GPCR, and one of the four prostaglandin E2 receptors sharing the 5p13.1 with *C9*. According to Germar et al., (2011), the role of *PTGER4* includes the activation of T-cell factor signaling, and development of T-cells, suggesting T cells are unique among hematopoietic cells, because development requires the thymus gland. Stem cells migrate from the bone marrow into the bloodstream and in the thymus gland, differentiate into T-cells. *PTGER4* also regulates the level and stability of cyclooxygenase-2 (COX-2) mRNA, works in the phosphorylation of glycogen-synthase-kinase-3 (GSK3), the enzyme that catalyzes transfer of glucose from UDPG to glycogen, which is stored in skeletal muscles.

Osteoporosis

Rodent studies indicate *PTGER4*, is involved in neonatal adaptation of circulatory system, osteoporosis, and initiation of immune responses in the skin. Osteoporosis, found in both sexes in MS, is often attributed to the use of glucocorticoids used to remedy inflammation. PGE2 is increased in the CSF and peripheral lymphocytes in MS; COX2 is expressed in the brain tissue within oligodendrocytes and microglia and/or macrophages (Palumbo, 2017). Non-steroidal anti-inflammatory drugs (NSAIDs) all act on COX.

G-PROTEIN COUPLED RECEPTORS

G-protein coupled receptor (GPR151) maps to 5q32 as the gene for an orphan member of the class A rhodopsin-like family of G-protein-coupled receptors (GPCRs), and a subfamily that includes somatostatin and opioid receptors. Activated G protein binds to, and activates numerous effector proteins, which generate second messengers that facilitate wide ranges of cellular and physiological processes. Members of this class of receptors play these roles: *C5AR1,* Complement C5, *ADORA3* Adenosine, *CCR2* Chemokine attracting monocytes, *CNR1* Cannabinoid receptor 1, *DARC* Receptor for malaria parasite, *DRD1* Dopamine receptor 1, modulating receptor 2, *EDNRA* Endothelin 1, peptide having a role in migraine, through a potent and long-lasting vasoconstriction, *EDNRB* Endothelin to generate a vasoactive second messenger, *FPR1*, Receptor for the protein mediating defensive response of phagocytic cells to invasion by microorganisms; important to inflammation, *GHSR* Growth hormone and body weight, *GRPR* Gastrin releasing peptide, involved in release of gastrointestinal hormones, smooth muscle cell contraction, *HCRTR2* hypocretin, feeding behavior, *HRH2* Histamine receptor 2, for GI motility and intestinal secretions, *HTR2B* 5HT receptor 2B, *HTR5A* 5HT regulating intracellular Ca2+, *HTR7* 5HT receptor for neuropsychiatric disorders, *MC1R* melanocortin 1 for ligand MSH, controls melanogenesis. Major receptor for determining sun sensitivity and genetic risk for skin cancers; 30 different alleles discovered. A mutation in loss of function biases towards red pheomelanin, instead of black eumelanin. The color phenotype is lighter hair and skin, subject to greater UV damage from lack of protection against ROS, *MC4R*,

melanocortin 4 receptor that binds with ACTH and MSH hormones. The only melanocortin receptor on astrocytes, *OPRK1* one of the receptors (k-opioid) which binds opioid compounds in the brain, mediating the effects, to alter pain, motor control, mood and consciousness, *P2RY6* pyrimidinergic receptor (DNA & RNA), *PTGIR* prostaglandin 12, binds with prostacyclin, the major product of COX in macrovascular endothelium, causing potent vasodilation and inhibition of platelet aggregation, *ADRB1*, adrenergic, beta-1-, receptor, whose polymorphisms affect the resting heart rate and are involved in heart failure, *ADRB2* adrenergic beta 2, polymorphisms, mutations or down regulations are associated with nocturnal asthma, obesity and type 2 diabetes. Astrocytes in MS have do not express this receptor, *HRH1* Histamine receptor 1, which mediates smooth muscle contractions, increase in capillary permeability due to contraction of terminal venules, release of catecholamine from adrenal medulla, and neurotransmission in the central nervous system, *CX3CR1* binds the chemokine which is involved in the adhesion and migration of leukocytes, *HTR2C* 5HT receptor 2C, whose RNA is edited in rodents subjected to stressful situations, *DRD2* Dopamine D2, GPCR inhibits the enzyme adenylyl cyclase, mutations linked to schizophrenia, *LTB4R* Leukotriene B receptor, *F2R* Coagulation factor II (thrombin) receptor, *MTNR1A* Melatonin receptor 1A, *GPR12* GPRC 12, *PTGDR* Prostaglandin D2 receptor, stimulates the enzyme adenylate cyclase resulting in elevation of intracellular cyclic AMP and Ca2+. Its ligand, prostaglandin D2 (PDG2), functions as a mast-cell derived mediator to trigger asthmatic responses. **G-protein coupled receptor kinase 6 (GRK6)** maps to 5q35.3 and phosphorylates the activated forms of GPCRs, initiating their deactivation. Doze & Perez (2012) state the importance of this class of receptors as targets for 30% of therapeutic treatments, binding neurotransmitters/neuromodulators, such as NE, DA and 5HT.The ligands, GABA, 5-HT, NE, and ACh inhibit action potential in neurons. More importantly, Doze & Perez refer to the offering of self-repair the GPCRs offer in neuropathological conditions, since these receptors are express on adult neural stem cells.

Metabotropic glutamate (mGlu) receptors

Spampinato et al, (2018) describe the cascade of neuroinflammation and excitotoxicity that leads to neuronal degeneration and death. Glial cells are part of the process because of their ability to upregulate or downregulate the events that lead to neuroinflammation, and neuronal damage, and when the system controlling glutamate is dysfunctional diseases result. The metabotropic glutamate (mGlu) receptors belong to GPCRs (5q32), existing on neurons and glial cells. Upregulation of the receptors is found on microglia, but more often on astrocytes (mGlu3), which leads to a pathway of neuronal death. Oliigodendrocytes express mGlu4, as well. Ikeshima-Kataoka (2016) found the upregulation of mGLUR3 can be co-localized with AQP4, therefore astrocyte mGLuR may play a role regulating extracellular glutamate levels. Forslin Aronsson et al., (2007) found astrocytes were less reactive, and neurons saved after excitotoxicity upon application of *a-MSH*.

Astrocytes receptors

Chromosome 5 expresses the loci for the receptors found on the surface of astrocytes - opioid, dopamine (DA), GABA, serotonin (5HT), B-adrenergic (B2-AR) (Temburni & Jacob 2001), and GDNF. Barres (2008) noted it was very likely the astrocytes were the primary supplier of GABA.

NE, EPI and immunity

Elenkov, et al., (2000) studied the "cross-talk" between the brain, spinal cord and the immune system, recognizing two pathways-the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system. Lesions of the anterior hypothalamus can depress both B cell and T cell immunity. The actions of EPI, and NE, act on immune cells through *ADRB2,* also found on the sympathetic neurons, which innervate the lymphoid organs, nerves of the spleen, thymus, bone marrow, and lymph nodes. NE is released by sympathetic nerve terminals in lymphoid organs, and further, stimulates the *B2AR*, which inhibits the production of pro-inflammatory cytokines, such as IL-12, TNF-alpha, and IFN-y by APC, Th1 helper cells, and stimulates the production of anti-inflammatory cytokines, such as IL10. NE and EPI both stimulate the production of Th2 anti-inflammatory cytokines IL10 and TGF-B. This suppression of Th1 response of cellular immunity produces a shift to Th2 dominance of humoral immunity. These authors felt the selective pharmacological manipulation of both the alpha (2) and beta (2) - adrenoreceptors held promise for autoimmune diseases, and chronic fatigue syndromes.

Adrenergic receptors

Yang-Feng et al., (1990) concluded the distance between the alpha 1- and beta 2-AR genes in human are within 300 kilobases (kb) of each other on chromosome 5, and were once a common receptor, which through gene and chromosome duplication, took on individual roles producing physiological effects by ligands, neurotransmitter NE and hormone EPI. Cagliani et al., (2009) indicated the *ADRB2* had distinct ethnicity-based variability among Europeans, Asians and Africans. Liberzon et al., (2014) discovered a polymorphism of ADRB2, following the occurrence of childhood trauma, related to adult PTSD. The **Adrenoceptor beta 2 (ADRAB2/ADRB2/B2AR)** maps to _5q32._ Expression of this GCPR affects the ligand-binding characteristic of the B1 adrenoceptor at 10q24-26 (Porcelli et al. 2011). RNA for the B1 receptor is found in tissues of the brain, heart (left ventricle), adipose, esophagus, cervix, and sun exposed skin.

Astrocytes in the brains of MS patients do not express the *B2-AR* (De Keyser et al., 1999). Zeinstra et al., (2002) reviewed the range of neurotransmitter receptors found in cultured astrocytes, knowing they discovered the B2-AR was absent on astrocytes in MS, and found other receptors were silent in chronic plaques in MS, including the dopamine (*D1)* and histamine (H1) receptors.

The lack of *ADRAB2* receptors on astrocytes in NAWM, or in any plaques created by astrogliosis in the MS brains, compared to those from ALS or strokes, led De Keyser et al., (1999), to hypothesize the lack of *B2-AR* might play an important role in the perpetuation, or induction, of autoimmune MS. These authors found class II MHC + reactive swollen astrocytes expressed on the edges of chronic active lesions, and concluded this phenomenon resulted from inflammation, but not as a primary occurrence. They questioned why myelin antigens in circulation of those healthy humans without MS, including victims of ischemic stroke, did not have MS demyelinating lesions, despite activated T-cells against myelin in their circulation, as in MS. De Keyser and colleagues concluded the lack of *B2-AR* as the defective endogenous suppressor mechanism in brain inflammation, as the ligand NE by binds to this receptor and is one of the suppressors that regulated astrocytic class II MHC expression (along with glutamate). Neurons did not show a lack of *ADRAB2*, as did fibrillary astrocytes of the NAWM, and reactive astrocytes in chronic active and inactive plaques. De Keyser, et al., (2004), reconfirmed the lack of B2-AR whose role is normally, via cyclic AMP, to inhibit MHC class II molecules, as well as stimulate the conversion of glycogen in astrocytes, suggesting further the defect may then allow the astrocytes to become the APC, which initiates inflammation, and also impairs the normal generation of lactate within astrocytes, which is normally transferred to axons as an energy source.

Sex differences in adrenergic receptor response

De Coupade et al., (2007) discovered a sex bias in rodents, in the *B2-AR* dependent mechanism on CD11a leukocytes expressing adhesion molecules, and concluded inflammatory responses based on B2-AR in male leukocytes might contribute to a sexual difference handling the stress of inflammatory disease. Kneale, et al., (2000) found NE caused less vasoconstriction in women than in men, associated with the *B2-AR* in pre-menopausal women, who had a greater response to vasodilators. Males exhibit a different course of MS than females.

MHC II

CD74 Antigen (invariant polypeptide of major histocompatibility class II antigen associated) CD74/DHLAG maps to 5q33.1 and is associated with class II major histocompatibility complex (MHC), playing a role in antigen presentation for the immune response. Konttinen et al., (1990) found MHC II antigen expression, IFN-y secretion, and IL2 receptor were similar in a twin study, where only one twin had MS. A meta-analysis of a genome scan, which identified new loci for MS was published in 2009 by a consortium repeating the underlying etiology of the dysregulated immune system in MS remains unknown (De Jager et al., 2009). The genes identified were IL12RA, *IL7R*, CD58, CD226, IRF8, and MHC class II.

Canine distemper

Canine Distemper Virus (CDV) once was considered in the cause of MS (Lincoln, Hankiewicz, & Cook (2008). Mutinelli et al., (1989) found CDV caused demyelinating lesions in the brains of dogs, with the main target of infection being the astrocytes. De Keyser et al., (2001) found dogs with CD encephalitis expressed *B2-AR* on neurons, but absent on astrocytes in acute and demyelinated lesions, and NAWM, the same situation as in MS, where astrocytes expressed MHC class II. These authors concluded this viral infection caused the receptor defect.

Memory

Gao, et al (2016) studied the *B2-AR* expressed on astrocytes in the hippocampus to be necessary for establishing long-term memory, and the release of NE as critical to create the arousal necessary for establishing long-term memory. Deletion of the *B2AR* gene influences the extracellular lactate, and glucose, of the hippocampus in the aged brain (Jensen et al., 2016**).** Martino et al., (2002) suggest raised lactate could be a sign also of the inflammation, local ischemia, and neuronal mitochondrial dysfunction. Albanese et al., (2016) associated lactate levels in the CSF of MS as an indication of disease progression.

Stress

NE is further involved in locomotion activity, blood flow and metabolism, as well as emotions. Stress symptoms can be relieved by turning off NE neurons in the CNS, as too much NE produces a severe stress reaction and too little NE can result in depression, and loss of pleasures. Mac Kenzie et al., (1976) described NE's effect on brain metabolism, both as an increase in cerebral oxygen consumption, and cerebral blood flow. The blood flow per unit of GM is four times that of WM, and the brain is very sensitive to blood or tissue gases. When inhalation of CO_2 is increased 5%, cerebral blood flow is increased 50%, as acid metabolites must be removed. The sudden adjustments allow regional cerebral blood flow to meet the demands for rapidly changing oxygen, and glucose metabolism that accompany brain activities such as learning. MS has shown some noticeable correlation to acquiring higher education.

Dopamine receptor

Jennings & Rusakov (2016) reexamined astrocyte-dopamine interactions, focusing on how DA affects the astrocytic intracellular signaling messenger, Ca2+, and evidence for astrocyte-mediated effects of dopamine on neurons. Immune cells produce DA, and DA affects T cell immune response, as receptors exist on T-cells and leukocytes (Arreola et al., 2016) with noted relevance in MS (Consentino & Marino, 2013).

Dopamine Receptor 1A (DRD1A) maps to 5q35.2 and is responsible for vasodilation, diuresis, and blood pressure decline. Rodents with impaired *DRD1A* saw a loss of sodium transport, and a development of hypertension. *DRD1A* is the most abundant of the dopamine receptors in the CNS. T-cells of MS patients show a shift in D1 (Levie,

Marino & Cosentino, 2017) and Sunahara et al., (1990) identified D1 receptors regulate neuron growth and differentiation, and through DA receptor mediated events, influence behavior.

Cannabinoid receptors

The CB1 receptor *CNR1* (*5q32*), expressed on almost all cells of the CNS. The CB1 mediates the release of glutamate by astrocytes at synapses. CB1 receptors are also found on the perivascular end-feet of astrocytes, which determine local blood flow in the brain (Rodriguez et al., 2001, cited in Scheller & Kirchoff, 2016).

The CB2, (1p36.11) receptor is strongly activated in microglia, and endothelial cells (Oliveira da Cruzz et al., 2016 cited in Scheller & Kirchoff, 2016). CB2 is more involved in anti-inflammatory effects (Buckley, 2008 cited in Scheller & Kirchoff, 2016) through expression by microglia (Schmole et al., 2015 cited in Scheller & Kirchoff, 2016). Microglia also interact with brain capillaries, and via the CB2, help maintain the integrity of the BBB (Ramirez et al., 2012 cited in Scheller & Kirchoff, 2016).

KERATINOCYTES, MELANOCYTES, MELANOGENESIS

Keratinocytes

Keratinocytes may produce catecholamines from L-DOPA, which is the precursor of melanin, and binds to the a1 (a1B, 5q32-34) and B2 (5q32) adrenergic receptors in melanocytes which stimulates melanogenesis. ***Fibroblast growth factor 10 (FGF10)****,* maps to 5p12 and aids cell division of epidermal cells of the skin in becoming keratinocytes. In rodents, this gene is required for embryonic epidermal cells to shape the brain. Itoh (2016) determined that *FGF10* is involved in the formation of tumors in pancreatic and breast cancers, and is a crucial paracrine signal for epithelium development, health and disease. *FGF10* is implicated as a primary factor in the process of wound healing, which is dysfunctional in diabetics, and accounts for some deaths in MS.

Endocannabinoid system

Videira, Moura & Magina (2013) investigated the role of the recently described cutaneous endocannabinoid system in melanogenesis, demonstrated UVR also activates endocannabinoid production by keratinocytes, and a paracrine CB1-mediated endocannabinoid signaling negatively regulates melanin synthesis (Mackie, 2006). Zagon & McLaughlin (2017) review enkephalin receptors located in keratinocytes, responsible for pain in the body, as well as the peptide B-endorphin resulting from cleavage of *POMC*, which binds to the opioid receptor for pain relief; enkephalin are low during relapse of MS. Dr. Candace Pert (Pert et al., 1986) highlighted the opioid receptor in her work on the psychosomatic network between neuropeptides and the body's endogenous opioids. Bhagavan & Ha (2015) noticed when B-endorphin is released with ACTH into the third ventricle in the brain, the brain noticeably changes. These authors confirm circulating B-endorphin, and encephalin from the adrenal

medulla, are the analgesics for stress. B-endorphin is chemically replaced by exogenous morphine.

Melanocytes

Melanocytes produce *POMC* (2p23.3) peptides, cytokines, NO, prostaglandins, and leukotrienes, which act either in autocrine, or paracrine fasion on keratinocytes and are involved in immune and inflammatory responses. Melanocytes interact with endocrine, immune, inflammatory and CNS systems, but activity is regulated either by UVR or by drugs. Melanocytes relate to nerve cells, as both originate from the dorsal ectoderm in the fetus, and melanocytes leave the developing nervous system, and migrate to help form the skin. The number of melanocytes determines ethnicity, as in the people of Kenya, who have an abundant number of melanocytes. Like nerve cells, melanocytes develop branching processes to attach to nearby cells in order to send pigment to these cells, coloring a large portion of skin from one melanocyte. The starting point for the pigment is tyrosine, which becomes L-DOPA, and then becomes either one of two types of melanin, the black/brown (eumelanin), or the red/yellow (pheomelanin) pigment formed by the conjugation of cysteine or glutathione. In the brain, the tyrosine converts to dopamine, which gives rise to neuromelanin, found in the substantia nigra. Eumelanin is the major type in individuals with dark skin and hair and is more efficient in protecting against harmful sun radiation. Pheomelanin is predominantly found in individuals with red hair and fair skin, in whom skin tumors are more common. Those with red hair make only a small amount of the driving enzyme tyrosinase (Wills 1994), however there are foods which contain tyrosinase to supplement, including cheese, soybeans, beef, lamb, pork, fish, chicken, nuts, seeds, eggs, beans, and whole grain.

Melanocyte receptors include muscarinic receptors (AChR), a- and B- estrogen receptors. As estrogen levels increase during pregnancy, hyperpigmentation occurs, expressing what is called the "pregnancy mask". Birthmarks are expressed in two processes- either tiny blood vessels or malformed pigment cells (Wills 1994).

Melanogenesis

Melanogenesis is the production of the pigment melanin in melanosomes by melanocytes. The thorough review by Videira, Moura & Magina, (2013), included the factors regulating skin pigmentation, the stages of melanogenesis (along with genetic defects), how melanocyte-keratinocytes interact, how the MC1R is activated by peptides MSH, and ACTH, cut from *POMC*, and how skin pigmentation is induced by UVR. Videira, Moura & Magina, described the dependence for melanogenesis upon several receptors, and different pathways. Melanin is produced when the skin absorbs the UVR from the sun, and sunlight is the most important extrinsic factor in the regulation of the process, and UVR is the main stimulus for induced pigmentation of the skin known as "tanning". Genetic factors determine two types of induced pigmentation. The first is immediate pigmentation occurring 5-10 minutes after exposure to UVA rays, quick to fade because it does not depend on increasing the synthesis of melanin, but on the

oxidation of pre-existing melanin. The second is delayed pigmentation occurring 3-4 days after exposure to UVR, mainly due to UVB radiation (vitamin D3), and lasts for weeks. This results from an increased level of melanin in the epidermal layer, particularly eumelanin. Eumelanin acts as a natural sunscreen against photo aging and photo-carcinogenesis, in part by reducing ROS, and increasing repair of DNA damage.

Phenotype and associations to MS

Poser (1993) reviewed the genetic factors that vary among ethnic groups, and singled out the rare amount of MS in black Africans, except the ones who mixed with the white population. Black Africans have the highest and largest melanosomes. Videira, Moura & Magina, (2013), noted literature to support the diversity in phenotypes of skin pigmentation, which results from the size and number of melanosomes. Melanosomes originate at birth, and are not influenced by sun exposure. The melanosomes of dark-skinned individuals are larger, more numerous, and elongated, which delays the degradation of keratinocytes, responsible for decrease in pigmentation.

Dolan's cluster study (2003) showed more than 50% of the MS cluster sample presented the phenotype of light hair, and blue eyes. Nordic phenotype shows red/blonde hair and blue eyes, and 90% of the Vikings of Poser's hypothesis (Poser 1994), had light eyes. The Vikings did integrate with the Jewish population through trade in the Kazarian area of the Black Sea. Khankhanian et al., (2015), Poser (1994), and Leibowitz & Adler (1973), noted the selectivity towards MS in the Ashkenazi Jewish lineage in Israel. Poser noted that 62% of the Palestinians have light colored eyes compared to only 21.6 % of the Kuwaitis.

Red hair is concentrated in Scotland, and mainland Scotland has the highest prevalence rates of MS found anywhere in the world (Rosati 2001). Murray (1976) mentioned the prejudice of fair hair, skin, and eyes to the risk of developing MS, and the Vikings had this phenotype (Montesano, 2012). Redheads were common in both Celtic and Germanic people. Ireland has the most redheads in the world, and suffered the most insanity, when mental disorders were being identified in Europe (Torrey & Miller, 2002). The MC1R is recessive in red hair, needing genes from both parents to present physically. MC1R is responsible for blue eyes, and congenital melanocytic naevi, a rare form of birthmark.

Puberty is associated with MS (Chitnis, 2013), and during puberty, the body produces more melanin evenly throughout the skin, and freckles should fade, but freckles may remain with the expression of red hair (Beam, 2019). Freckles are clusters of concentrated cells full of melanin, resulting when melanocytes overproduce melanin granules and are most common to Northern Europeans. Freckles are an indication that the normal readjustment of melanin in the skin did not occur and arise with red hair.

Premature graying of hair is largely genetic. Hair follicles contain both melanin-producing melanocytes, which gives the hair color, and melanocyte stem cells (McSCs). When the body stops generating melanin, hair turns gray, silver or white. Chou et al.,

(2013) found stress from UVB radiation, and wounding of the skin, upregulated MSH and ACTH. The McSCs migrated from hair follicles to repair the epidermis via the MC1R, and resulted in loss of pigmentation in the hair follicle. Since ligands for the MC1R include the stress hormone ACTH, they concluded this might indicate the pathway between stresses and lose of hair color. Chronic fatigue syndrome (CFS) patients of less than 5 years had significantly higher levels of MSH in their peripheral blood according to Shishioh-Ikejima et al., (2010). Demitrack et al., (1991) found impaired HPA axis activation in CFS.

Melanocortin receptors-MC1R and Neanderthals

Videira, Moura & Magina, (2013) identified melanocortin receptors as *GPCRs* (5q32), and are stimulated by the same levels of ultraviolet rays (UVR) that stimulate melanogenesis by the liberation of nitric oxide (University of Southampton, 2014). The MC1-R predominates in melanocytes, and its agonists include *α-MSH* and *ACTH*. The MC1R is found in immune cells, including macrophages and leukocytes, where it mediates the anti-inflammatory action of α-MSH in leukocytes (Catania 2007 in Caruso et al.).

Polymorphisms of the MC1-R are responsible for ethnic differences in skin pigmentation response to exposure to UVR. Activating the MC1R by the *POMC* peptides causes an accumulation of eumelanin (brown or black hair), instead of pheomelanin in the skin. There is a high incidence of MC1R mutation in individuals with red hair and light skin and may be responsible for a decreased response to α-MSH, resulting in decreased eumelanogenesis, and reduced pigmentation induced by UVR. The first Neanderthal fossil discovered in 1856 in a cave near Dusseldorf, Germany, represented a group who expressed a mutation of the MC1R gene. Neanderthals had the phenotype of blonde and red hair from the production of pheomelanin. Twenty-percent of DNA from Neanderthals survives in modern humans, and is expressed in skin, and hair (Hajdinjak, et al., 2018).

MC4R, astrocytes and inflammation

The MC4R gene is expressed predominantly in the brain (Mountjoy et al, 1994), although also detected in adipose tissue, where it has a role in glucose regulation (Chhajlani 1996). In 1984, the MC4R were discovered to be the only receptor expressed on astrocytes (Evans et al, 2004 cited in Caruso et al, 2013). Carniglia et al., (2013) found binding of MSH decreases pro-inflammatory mediators, and increases BDNF expression. The activation of MC4R increases secretion of anti-inflammatory IL10 from microglia, but not in astrocytes. Carniglia et al., (2016) describe a-MSH role in microglia, inhibiting the receptors involved with inflammatory cytokine production (TLR2 and TLR4), responsible for activating the innate immune system.

Pain and Agouti

MC4R specifically relates to nociceptive pain through nerves of spinal cord, and AGRP can inhibit the melanocortin system from coping with overactive nociceptive nerves (Bertorelli et al., 2005 cited in Caruso et al). Red haired individuals are subject to feel more pain. Sharma et al., (2006) found topical application of a selective MC4R agonist was neuroprotective in spinal cord injury, concluding MC4R is involved in the neuroregenerative effects of melanocortins. Agouti signaling protein (AGRP) regulates pigmentation by restricting eumelanin by competing with a-MSH for receptors, and results in the production of pheomelanogenesis, blonde or red hair. AGRP is also present in the brain, but only in neurons in the area of the hypothalamus adjacent to the third ventricle (Dinulescu & Cone 2000) where it acts as a competitive antagonist of MC3R, and MC4R.

Fever

Sinha, Schioth, & Tatro, (2003), concluded MC4R mediated antipyretic effects, inhibited fever and production of body heat, using LPS to increase body temperature through peripheral vasoconstriction. Catania & Lipton (1998) earlier published the modulation of fever, and inflammation, in the brain by a-MSH affecting TNF-a, and NO, release from microglia. These authors further studied properties of a-MSH to regulate fever, and inflammation, aid in strokes, and perhaps inhibit the inflammatory agents TNF-a and NO in microglia, and TNF-a in astrocytes, based on glia secreting a-MSH and expressing receptors, in an autocrine manner (Catania et al., 2006). Caruso et al., (2010) showed MC4R expressed on hypothalamic neurons, stopped the production of TNF-a, and IFN-y, caused by LPS, and further conclude MC4R is involved in the anti-inflammatory effects melanocortins have in the brain.

Obesity, leptin, insulin and melanocortin receptors

The environmental susceptibility for MS is determined to be associated with increased body mass index (BMI). Leibowitz & Adler (1973) noted per-capita calorie consumption was related to the etiology of MS, and attributed the greater number of calories consumed in the developed world to be the effect diet had on MS. Gianfrancesco & Barcellos (2016) reviewed obesity in association with MS, referring to the worldwide studies demonstrating early childhood and adolescent obesity were significant risk factors for MS.

BMI fat mass and fat cell volume associates to locus 5q31-32 and the gene *FGF1* (5q31.3) associates with an excess intake of nutrients. *POMC* (*2p23.3*) neurons in the brain suppress appetite. Xia & Grant (2013) include *POMC* and leptin expression, in the genetic review of human obesity, with the disruption of MC4R leading to severe obesity. Fisler & Warden (2013) describe how *a-MSH* regulates food intake by the MC4R, in addition to the pigmentation of hair, and by studying obese, yellow-coated rodents determined both results were caused by agouti (AGRP) inhibiting the binding of a-MSH to receptors. B-MSH also plays an important role in weight regulation through the

MC4R, and maintains the balance between energy from the intake of food and energy expended by the body. The MC3R and MC4R are highly expressed in the hypothalamus for appetite control, and if mutated causing genetic disruption in the leptin-melanocortin pathways, the MC4R effects the occurrence of younger onset obesity. The MC4R is significant in decreasing lean body mass, increasing fat mass, and decreasing mineral density in bone, caused by genetic disruption (Farooqi & O'Rahilly, 2005; Clifton et al., 2017). Lotta et al, (2019) determined variants of the MC4R protected against obesity. Oksenberg & Barcellos (2000) noted that those with MS have more frequent bone loss than controls.

Caruso et al., (2007) remark obesity implies a high fat diet, citing the study by Gregor & Hotamisligil (2011) in which the local immune response of chronic obesity created inflammation, and disrupted both insulin and leptin. Both leptin and insulin act as adiposity signals, as blood levels increase in proportion to body fat mass, while in the brain, these hormones promote negative energy balance (Caruso et al., 2013), and both are inhibited by AGRP neurons. The inflammatory cytokine IL-6 is produced and secreted by adipose tissue mass, and is known to be inflammatory to monocytes and macrophages (Purkayastha and Raven, 2011). Hsuchou et al., 2009 discovered leptin receptors on astrocytes in the hypothalamus, and noted an increase in expression when a high-fat diet leads to obesity. Matarese et al., (2005), discovered an increase of leptin in both blood circulation, and CSF in MS correlated to a reduced number of CD4+CD25+ Treg. Taylor & Namba, (2001) found *a-MSH* binding at MC5R mediates this class of T cells.

Pro-melanocyte concentrating hormone and variants

Pedeutour, et al., (1994) related both the authentic gene for the neuropeptide PMCH, and the two variants found on chromosome 5, to disorders of the brain. **Pro-melanin concentrating hormone like 1 (PMCH1)** maps to 5p14.3, as a pseudogene for PMCH, whose functional gene (locus 12q23-q24; 12q32.2) stimulates hunger, and may regulate energy homeostasis, and promotes sleep. A second variant of pro-melanin concentrating hormone**, pro-melanin concentrating hormone like 2 (pseudogene) (PMCHL2)** maps to 5q12-13. Pink et al., (2011), reviewed ways in which pseudogenes exert their effect on coding genes, exploring the role of pseudogenes in the complexity of noncoding RNA, which contributes to normal cellular regulation. Pseudogenes have been considered "junk" DNA, and failed copies of genes arising during the evolution of genomes. Recently some pseudogenes appear to have the potential to regulate their protein-coding cousins. Many pseudogenes are not silent, but are transcribed into RNA, some exhibiting a tissue-specific pattern of activation. Pseudogenes are capable of regulating tumor suppressors and oncogenes by acting as microRNA decoys. The often-deregulated pseudogenes occur during cancer progression.

Feeding and body mass

PMCH regulates feeding behavior and energy balance by causing an increase in eating, increasing body mass. When melanocyte-concentrating hormone (MCH) is increased in olfactory regions of the brain, there is an increased desire for fatty foods.

Melanocyte concentrating hormone and skin cancer

MCH is an antagonist to MSH, and has two receptors-MCHR1 (mammals and melanocytes) and MCHR2 (humans and dogs). Human melanocytes express the receptor MCHR1, antagonizing a-MSH, lowering the amount of melanin produced, and regulating skin pigmentation. MCH promotes melanoma and squamous cell conditions of the skin in this antagonistic role to a-MSH.

Sleep

PMCH regulates sleep, the wake cycle and mood, and all are disrupted in MS. MCH promotes longer duration of REM sleep in the sleep cycle, the length of sleep, and is involved in narcolepsy (Torterolo 2007). Sleep conserves energy. Glucose controls sleep, as high amounts of glucose and glutamate cause firing of the MCH neurons. It is normal for acute bacterial infections to decrease glucose concentrations, but in chronic disease, the pathway to the reduction in glucose observed remains a mystery.

Stress and mood

Presse et al., (1992) found this cyclic neuropeptide may be involved in the control of the HPA axis, and further "goal-oriented" behavior and homeostatic functions. The neurons for MCH are found in the hypothalamus, and stimulates *ACTH* in the HPA axis of rodents. Gold et al., (2010) found evidence that shrinkage of the hypothalamus in the brains of those with MS may correlate to the symptom of depression. In animal models, Bhagavan & Ha (2015) determined mature rMCH mRNA exists in the dorsolateral hypothalamus, and originates in the embryo at 18 days, and rises most at weaning to finally reach its constant level adulthood. Stress causes a decrease in this mRNA following 1-3 days of stress, but returns to normal by 7 days. Glucocorticoids appear to work to restore the rMCH gene activity. MCH mRNA is extremely reduced in dehydration, or chronic salt overload. Nourbakhsh et al., (2016) linked dietary salt to relapse in pediatric MS.

The MCH role in depression is via the MCHR1. Miller et al., (2009) studying genetics in an association between schizophrenia and bipolar, determined variations in the MCHR2 and the MCHR1 genes had roles in both disorders. Two pathways showed relevance, and these authors called for more investigation of the interaction between the melanotropin receptors and the tryptophan-based kynurenine pathway.

SYMPTOMS

The number of variable symptoms expressed in MS escapes complete understanding, and no two people have the exact combination. As a result, MS patients take a

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multitude of pharmaceuticals. The symptoms of MS are both sensory (optic neuritis, gait ataxia, limb weakness, neurogenic bowel/bladder, etc.) and cortical (aphasia, recurrent seizures, visual-field loss, etc.). In brain matter, GM loss correlates to verbal memory, euphoria and disinhibition, and WM loss to mental processing speed, and working memory (Sanfilipo et al., 2005), with some white matter lesions causing physical and cognitive disability. Optic neuropathy, which often occurs at the onset of MS, is an ischemic, stroke-like event, which damages the optic nerve.

Pain

Beside neurons, both astrocytes (Watkins, Milligan & Maier, 2003) and microglia (Schomberg & Olson 2012) are thought to contribute to the sensation of pain. Carniglia et al., (2017) concluded microglia play a role in pathological pain, through their response to neuropeptides derived from *POMC*. Wieseler-Frank, Maier & Watkins, (2004) determined pathological pain is amplified by acute pain and is regulated by microglia and astrocytes and the pro-inflammatory cytokines they secrete. Cannabinoid (CBD) currently serves as a possible aid in relief of pain.

Auditory hearing

Poser, in his *An Atlas of Multiple Sclerosis*, noted an acute, partial, hearing loss appeared on an audiogram of a patient with MS (Wills 1994). ***Very large G protein-coupled receptor 1 (VLGR1)*** maps to 5q14-q15 and links to the normal development of cochlear hair bundles (Mc Gee et al., (2006), and connects to the sense of hearing (Mc Millan et al., 2000-2013). Following exposure to noise, these hair bundles experience damage, and long-term loss appears to be the result of continued formation of ROS/RNS (Yamashita et al., 2004). Montesano (2013) hypothesized the toxins affiliated with artillery fire, might be involved with the risk of developing MS, and noted the history of the Salpetriere in Paris, being an arsenal prior to becoming an asylum for females afflicted with physical, and emotional, disorders. Noise stress is experienced in a soldier's training and performance. As the author described in *War, Love and Peace*, soldiers were also susceptible to dust particles, often in their eyes, mouth and ears, with little opportunity to shower the particles off. Sudden hearing loss is thought to be partly due to vascular pathology involving fibrinogen (Rudack et al., 2006). Melanin is found in some cochlea cells of the inner ear and may protect against hearing loss.

Taste

A change in taste is a symptom appearing in relapsing-remitting MS. ***Hyperpolarization activated cyclic nucleotide gated potassium channel 1 (HCN1)*** maps to 5p12 and is associated with "sour" taste. More importantly associated with MS is the role of *HCN1* as part of the potassium (K+) channels found on neurons and in the heart. Dalfampridine (AMPYRA) works for some patients with MS, and does so by blocking the potassium channels on the surface of nerve fibers, improving conduction along an axon with damaged myelin.

Smell

Uecker et al., (2017) concluded olfactory dysfunction is a symptom in MS patients, and may indicate disease progression. These authors cite the processing for discrimination of odors occurs in higher central regions of the CNS, and olfactory dysfunction could be due to CNS damage. The olfactory receptor gene family is the largest in the genome.***Olfactory receptor family 4 subfamily F member 3 (OR4F3); Olfactory receptor family 2 subfamily 1&2 (ORV1, ORV2)*** map to 5q35.3 as receptors in the nose that bind odors, and initiate the neuronal response that triggers the sense of smell. They are members of *GPCR* (5q32).

The nose-brain barrier depends on intact epithelia with tight junctions, and xenobiotic metabolizing capacity, for the process of working with inhaled toxins, and particulate matter. Calderon-Garcodienas et al., (2002) studied the ability for air pollution to enter the blood circulation through the nose.

Cognitive and emotional difficulties

The drugs KLONOPIN, VALIUM, XANAX and ATIVAN supply gamma - Aminobutyric acid (GABA). BACLOFEN binds to the GABA-b receptor. All are prescribed to help MS symptoms. The cluster of GABA receptors mapped to 5q31.1-q33.1 is extremely intriguing, given Sanfilipo et al (2006) identified the possibility euphoria, and disinhibition experienced in MS may be the result of loss of GABA neurons, which provide widespread inhibitory effects in the cortex of the brain.

Cottrell & Wilson (1926) challenged the treatment of disseminated sclerosis to neurology, favoring psychiatry, as various symptoms of mental disorder occurred before the development of the physical signs of MS. Schizophrenic type behaviors were among the noted conditions found in patients in 1920's London, and it was hypothesized the psychoses, and psychoneuroses, were caused by some toxin, perhaps a virus, originating in the CSF, or the central arterial system of the brain, and affecting the lining of the ventricles. Ombrediane (1929) observed changes in mood, cognition, dementia, and psychosis in his hospitalized MS patients in Paris, but did not see a correlation to the plaques, and therefore professed the neuropsychiatric changes were a "diffuse toxic state" (Murray, 2005 cited in Montesano, 2012). Sadovnick et al., (1991) noted MS has a higher suicide risk than other chronic conditions, even in the young MS patients with mild symptoms. Zorzon et al., (2001) discovered the anxiety disorder common in MS has not correlated significantly with regional or total lesion loads, or with atrophy of the brain in patients.

Gamma-aminobutyric acid GABAA receptor (GABAA) belongs to a heterogeneous family of receptors of GABA, the major mediator of inhibitory transmission in the CNS (Mc Kernan & Whiting 1996). Mac Dermott et al., (1999) reviewed GABA receptors expressed on presynaptic terminals of neurons. An upregulation of this receptor links to the condition of schizophrenia (Benes et al, 1996). Fuks et al., (2012) concluded that *T. Gondii*, which infects leukocytes, dysregulates both GABA and the receptor, to influence

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immune system behavior. GABA relates to obsessive-compulsive disorder (OCD), with behaviors of hoarding, anxiety and panic disorders. Algin et al., (2010) found panic disorder in MS to be the primary symptom of a new demyelinating episode.

The neurotransmitter dopamine (DA), when dysregulated, brings upon physical symptoms, such as in tremor, and psychological symptoms. The ***dopamine transport 1 (DAT1)*** is mapped to 5p15.3. DA can relate to fatigue, attention deficit disorder (ADD), bipolar disorder (BD), schizophrenic disorder (SZD), and Parkinson's disease (PD) (Habak et al., 2014). Patel et al., (2018) determined females with BD had higher risk of comorbidity with other inflammatory conditions such as asthma, Crohn's disease and MS. Piaggio et al., (2018) reviewed the similarities in neuroimaging, and immunology between the manic phase of BD, and MS, in early stages of activity, and found both had white matter (WM) alterations in the corpus callosum.

Bowel disorders

Jean-Pierre Hugot, MD, PhD (1934), labeled Crohn's (IBD) as familial, with non-Mendelian traits, caused by a complex interplay between the environment and many genes, each one having limited individual impact. IBD is relapsing/remitting, with an unknown etiology, caused by genetics, the immune system and environment, interacting together in a genetically predisposed person. Environmental factors, many psychological, triggers the immune dysfunction. Both gastrointestinal physicians and psychiatrists in the 1930s treated Crohn's disease (CD) patients, as exacerbations occurred with emotional life events and experiences**.** Sajadinejad et al., (2012) reviewed the positive association between stressful events and psychological triggers, as both CD and ulcerative colitis (UC) are affected by psychological stress. Personality, and the person's ability to cope with stress, makes IBD a psychobiological condition. The mechanisms of the brain/gut axis, and corticotrophin-releasing hormone (CRH) from psychological stress affecting motility and abnormal pain.

Depression and anxiety can precede CD, much like MS. Personality traits common in bowel disorders include neuroticism, perfectionism, difficulty describing or expressing feelings, distress through introversion, shame, and are risks for the comorbidity of anxiety, which occurs in 29-35% of IBD patients. The stress of the cytokines produced from smoking also appear to affect IBD, in concordance to MS.

The gastrointestinal tract is the source of 95% of the body's serotonin (Sanger, 2008 cited in Richard et al., 2009). Serotonin (5HT) is a vasoconstrictor. ***5-hydroxytryptamine receptor 1A (HTR1A)*** maps to 5q12.3, as one of the 14 receptors for 5HT. Kirchgessner et al., (1996) found an abundance of immunoreactive 5-HT1A receptors on nerves of the gut and pancreas. Stasi et al., (2014) concluded dysregulated 5-HT signaling via receptors both in the gut, and the CNS, contributes to the hypersensitivity of irritable bowel syndrome (IBS*). **5-hydroxytryptamine receptor-4 (HTR4)*** mapped to 5q32, is involved with both IBS and constipation. MS patients suffer

with many gastrointestinal problems (Levinthal et al., 2013) and constipation is the most common bowel complaint in MS (Lindsey & Wolinsky, 2003).

Natarajan, Northrup, & Yamamoto (2015) concluded chronic, unpredictable stress caused changes in the brain's 5HT system, altering the hypothalamus, which both induces CFS, and alters the mechanism behind long lasting thermoregulatory deficits, such as reaction body temperature reduction to cold stress. Porcelli et al (2011) reported desensitizing *HTR4* in rodents increased anxiety and reduced exploratory locomotion. Freedman (2002) discovered this receptor closely resembles the *beta-adrenergic receptor*, and directly affects neuronal development. It may cause childhood anxiety disorders if the gene is inactivated in childhood, and later in life, the adult exhibits irreversible persistent anxiety disorders, which has a 20% comorbidity of suicide**.** The dysregulation of 5HT is related to both cerebellar symptoms of MS (Monaca-Charley et al., 2003) and migraine headaches, which can occur at the time of relapse (Sandyk & Awerbach, 2009)**.**

Serotonin derives from tryptophan, catalyzed by the enzyme tryptophan hydroxylase. Karu et al., (2016) described the relation between the metabolism of tryptophan, inflammation, stress markers, and psychological and cognitive functioning, mentioning the kynurenine pathway. Large doses of tryptophan decrease the production of EPI and NE from acute stressors.

Tryptophan hydroxylase (TPH2) maps to 2q21.1, (same arm as STAT4 and IL1A) and variants of the gene associate with depression, suicidal behavior, ADHD and OCD. *TPH2* mRNA is regulated by glucocorticoids (Porcelli et al. 2011). Lightman (2008) reviewed the plasticity of the stress response using *TPH2* as the biomarker. The release of CRH is rapid in acute stress, but reduction is seen after chronic stress. This author discusses the CRH, *POMC*, *ACTH*, glucocorticoid pathway, with cortisol being released in a "pulsative ultradian pattern" of the normal circadian rhythm. Pulses increase with chronic stress. In the neonatal stage of life, environmental influences can alter this homeostatic ultradian rhythm, through receptors on tissue, including the *GRL* (5q31). Also DNA can be affected by epigenetics, and tissue response to GLU is altered. Neonatal alteration in levels of CRH and GRL regulation is accompanied by behavioral responses to stress. The 5HT pathway in the brain stem also alters outputs for expected future demands. Kim, Park & Hwang (2002) found this biopsychological dysregulation could be readjusted using sertraline (Zoloft) and fluoxetine (Prozac). Smoller et al., (2005) associated the CRH gene with childhood panic disorder.

Vitamin B6 helps convert tryptophan into 5HT. Willett (2001) suggests we acquire B6 in our diet mostly from fortified breakfast cereals, and in Dolan's cluster study (2003), it was breakfast cereal eaten during developmental ages, which appeared protective against adult onset of MS.

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IMMUNOMODULATION AND ANTI-INFLAMMATORY TREATMENTS

Neuropeptide Y

Delgado, M. (2013), reports treatment with neuropeptides VIP, *MSH*, NPY, and ghrelin decrease disease frequency, and severity, in animal models of RA, IBD, MS, IDDM1, and uveoretinitis. The pathways are impaired development of self-reactive Th1/Th17 cells and release of inflammatory cytokines/chemokines-TNFa, *IL12,* IL6, IL1B, and PGE2 by decreasing COX2, and increasing IL10 by macrophages, microglia, and dendritic cells. The production of pro-inflammatory cytokines, NOS, and matrix metalloproteinase are reduced with application of these peptides. **Neuropeptide Y receptor Y6 (NPY6R)** pseudogene receptor for NPY, maps to 5q31.2. NPY is involved in physiological and homeostatic processes in both the CNS, where it is the most abundant peptide present in the mammals, as well as the PNS. NPY is secreted alongside other neurotransmitters like GABA and GLU. NPY is known to be involved in the stress response, and the University of Michigan (2011) discovered a link between the gene for NPY and depression.

Proopiomelanocortin (POMC) maps to 2p23.3 and is synthesized mainly in the corticotroph cells of the anterior pituitary, but also in tissues of the hypothalamus, placenta and epithelium. *POMC* is not regulated by CRH, or glucocorticoids, but by dopamine (DA) (Bhagavan & Ha, 2015. *POMC* is cut into peptides, with functional differences, including those involved with pain and energy homeostasis, melanocyte stimulation and immune modulation). *POMC* is the precursor to *ACTH*, and the melanocortinis- a-MSH, B-MSH, y-MSH and B-endorphin-all relevant to pathways in MS *POMC* is affected by the drugs naltrexone/bupropion.

Caruso (2013) described *POMC* neurons projecting throughout the brain. Bertolini, Tacchi & Vergoni (2009) thoroughly reveiw the extra-hormonal and pharmacological brain effects of melanocortins. Melanocortin peptides are documented as anti-inflammatory and neuroprotective (Catania et al, 2008). As previously, only MC4R exists on astrocytes, and it modulates functions (Caruso et al., 2013). Caruso et al., (2007) found the MC4R on astrocytes protects the astrocytes from apoptosis induced by LPS & IFN-y. MSH stimulates cAMP production, and Fedoroff et al., (1987) found by applying an analog of cAMP to astroblasts, premature astrocytes could be manipulated to resemble reactive astrocytes in their organization of microfilaments.The reactive astrocytes Barres (2008) identified as the producers of inflammatory secretions, Caruso and colleagues also contend have a role in brain pathology, and can lead to disease states, in agreement with Barres. Both authors concluded the manipulation of the reactive astrocyte is the goal, and activation of MC4R may restore the functionality of astrocytes, and lessen inflammatory disorders and neurodegenerative disease.

Adrenocorticotropic hormone

ACTHAR gel is a corticotropic injection used to treat MS relapses in adults. ACTH is one peptide, which binds to MC2R and stimulates the release of the stress hormone

cortisol. CRH stimulates the adrenal glands to release cortisol from the adrenal cortex during stress, activates the mast cells in the endothelium, and makes the BBB more permeable. Cortisol, a member of the glucocorticoids, maintains blood sugar during stress, and stops inflammation. Lack of cortisol stimulates the HPA-axis, causing release of *POMC,* which forms ACTH, MSH and causes hyperpigmentation by increasing melanin in melanocytes.

Melanocytes-stimulating hormone

MSH production and secretion is part of the stress response (Borysenko & Borysenko, 1982). MSH is a neuropeptide, which regulates the inflammatory response by directly down regulating cytokines, TNF-a, IL-12, IL-6 and IL-1B and various chemokines, PGE2, NO, and the late inflammatory mediator in macrophage. It appears that IL-12 upregulation is part of the initiation of MS (Windhagen, Newcombe & Dangond, 1995). TNF-a significantly increased the day following a psychological stressful event (Lalive, Burkhand & Chofflin, 2002 cited in Dolan, 2003).

Alpha-MSH

Keratinocytes and melanocytes are mainly responsible for the a-MSH production in the skin (Videira, Moura & Magina, 2013). A-MSH stimulates melanocyte to produce the brown pigment, melanin, determining the color of a person's skin, hair and eyes. Van der Mei et al., (2003) noted fair skin was associated with a higher risk of MS. A-MSH binds to the MC1R receptor

The antimicrobial properties of a-MSH, VIP, and ghrelin against gram-positive and gram-negative bacteria exist mostly in the GI tract, and are important to the conditions of bowel disorders, such as Crohn's disease (Scully, 2014). Gram-negative bacteria cause urinary tract infections (UTI) common in MS

Pregnancy

The state of pregnancy is known to be a time of inactivity in MS. One biological change during the last 3 months of pregnancy is the conversion of tryptohan to niacin- based vitamin B3 more efficiently than in a non-pregnant state (Wertz et al., 1958).

Gamma-aminobutyric acid Type A receptor pi unit (GABRP) maps to 5q35, the GABA receptor found in the uterus and ovaries and binds the steroid pregnenolone, producing progesterone, DHEA and estrogen. Estrogen can stimulate the CRH gene to promote secretion of cortisol in pregnancy. CRH in the placenta and lining of the uterus prevents the mother's immune system from rejecting the early fetus, declines post-delivery, and associates with postpartum depression.

Corticotropin-releasing hormone binding protein (CRHBP) maps to 5q13.3, and is a source of the inactivation of CRH. CRH stimulates the production of *POMC.* CRH increases throughout pregnancy, but the production is from the placenta. CRH falls rapidly after delivery, so the role of *CRHBP* in pregnancy is to prevent pituitary-adrenal

stimulation. *POMC* in the placenta is not inhibited by glucocorticoids, does not correlate to ACTH or cortisol in circulation, and responds only to CRH levels (Penn, 2017). Raffin-Sanson et al., (1999) discovered during pregnancy, *POMC* is derived exclusively from the placenta, with no influence from the pituitary, to be released physiologically, thus making *POMC* a marker for pregnancy. B-endorphin levels, derived from *POMC*, increase during pregnancy, with the most elevated levels during labor and delivery (Zagon & McLaughlin, 2017). Wei & Lightman (1997) found the B-endorphin response to CRH took greater time in RRMS, compared with other forms of MS. Estradiol was low in 25% of pre-menopausal females, and testosterone 24% in males with MS. These authors concluded activation of the HPA axis in MS was secondary to active inflammatory stimuli.

The downregulated activity of MS at the time of pregnancy, also associates with the increase of a-MSH, another cleaved peptide from *POMC*, which increase the production of melanin, causing the pregnancy 'mask."

Hematopoietic stem cells and hematopoiesis

Genes on chromosome 5 control hematopoietic stem cells, and these stem cells have been experimented with to aid the progressive stages of MS. Hematopoiesis is controlled by chromosome 5. **The 5q-syndrome** (Van den Berghe et al, 1974) denotes the gene cluster localization at 5q31, which includes the interleukins**, colony-stimulating factor (*CSF2*),** and **granulocyte-monocyte colony-stimulating factor (*GM-CSF*)**. All play a role in the development of stem cells into white or red blood cells (hematopoiesis). Within the syndrome fall the conditions of anemia, normal or high platelet counts, and other dysfunctions in the bone marrow, including leukemia. Van Leeuwen, et al., (1989) added *IL4* (5q23.3-31.2) to the gene cluster of hematopoietic growth factors *IL3, IL5, GM-CSF (*5q23-31) because of closeness in distance, but endothelial cell growth factor (ECGF) at 5q31, did not appear close. The cytokine, *colony stimulating factor 2 (CSF2)* signals, and controls the proliferation, differentiation, and functional activation of the hematopoietic cell, including the precursor cells of macrophages, and granulocytes. De Kleer, et al., (2014) describe the subgroups of leukocytes, including granulocytes, monocytes, macrophages, and dendritic cells, originating from myeloblasts in the bone marrow, and thus termed myeloid. *CSF2* is connected to acute myelogenous leukemia.

Nutrition

The debate on the positive effects diet may have on the disease course of MS has remained controversial since the first MS diet was recommended by Swank in the 1950's. However, given the genetic focus of this genetic review, and the New Scientist article (2005) revealing food can change your genes for life, based on the concept of epigenetics, the following are some nutritional guidelines that may be given consideration.

Cohen, (2013) concluded migraine headaches are a result of sick or struggling mitochondria, suggesting supplementation with CoQ10, Mg+, B2, L-carnitine, and selenium may provide relief of this dysfunction.Matthews et al., (1998) concluded the antioxidant coenzyme Q10/CoQ10 (ubiquinone), increased the concentration of mitochondria in the brain, and is neuroprotective. Post-polio syndrome patients were treated with oral coenzyme Q10, in addition to creatine monohydrate.Ross, Chen & Ma, (2011) concluded vitamin A serves the production of melanin, and along with retinoic acid, regulates B-cell development and antibody production. Richard et al., (2009) identified the essential amino acid tryptophan has a role not only in synthesis of serotonin (5HT), but also in the kynurenine pathway, affecting mood and behavior. The body stores very little tryptophan in the tissues, so dietary sources were encouraged, as a potential therapy in psychiatric disorders. Attias et al., (1994) found oral magnesium reduced permanent hearing loss caused by exposure to noise. The potent supplement N-acetyl cysteine (NAC) also proved helpful in males who suffered hearing impacts from noise (Lin et al., 2010 cited in Ciuman, 2013).

Zinc displacement may explain how zinc metabolism can be impaired in multiple sclerosis, even though zinc levels are not always low (Wong et al., 1980; Palm & Hollmans, 1982). The heavy metals most implicated in MS--dental mercury (Baasch 1966), lead in gasoline (Ingalls,1983) (lead works through AQP4 to increase water permeability, as does CO2 and NH3), and industrial zinc (Stein et al.,1987) -all displace endogenous zinc from enzymes (Schroeder 1956; Taniguchi et al.,1975; Brandao-Neto & Bell 1994 cited in Peter Good). Astrocytes buffer essential metals like lead, mercury, and copper (Dolan, 2003), and despite being the hardiest of the neuroglial cells, astrocytes are sensitive to lead. Astrocytes enlarge in size and number, even when an injury is nonlethal. Fibrous astrocytes increase their intermediate filament, and when their cytoplasm is involved, astrocytes enlarge to a massive size, as in the lesions following a stroke, or those in MS. Zinc makes astrocytes resistant to swelling (Ashner et al, 1998 cited in Dolan 2003), as zinc also stabilizes the association of MBP with brain myelin membranes (Riccio, Giovannelli, & Bobba, 1995). Mercury causes the swelling of astrocytes, perhaps because it reduces the aquaporin water channel (AQP) (Hirano et al., 2010).

Alcohol antagonizes the action of glutamate (GLU) at the N-methyl-D-aspartate (NMDA) receptors and long-term potentiation decreases in the hippocampus, affecting memory and cognition. Alcohol increases levels of GABA, and eventually will cause a to pass out. Dietary measures which increase the production of serotonin (5HT) will help alcoholics. Naltexone decreases the craving for alcohol.

Dietary PUFAs and Cannabinoids

The brain is limited in its ability to synthesize long-chain PUFA. Polyunsaturated fatty acids (PUFAs) are the source for synthesis of prostaglandins (PG) and leukotrienes (LT).

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Caruso et al., (2013) citing Luo, Lang & Miller, (1998), state astrocytes synthesize higher levels of prostaglandins than neurons. Barres (2008) identifies that astrocytes secrete this unique lipid, along with supplying ATP and D-serine. What astrocytes can not supply in lipids, dietary sources appear to.

The essential fatty acid linoleic acid (Omega-6), found in most vegetable oils, is the major precursor for arachidonic acid (ArAc), which then leads to creation of prostaglandins. ArAc make a significant contribution to inflammation.Coconut oil prevents the transformation of omega-6 acid to ArAc.

Omega 3 (a-linolenic acid) PUFAS are the pathways to eicosapentaenoic acid (EPA), a component of fish oils, which is also the dietary source for docosahexaenoic acid (DHA), which contributes to brain health. EPA is the pathway to the leukotriene, LTD5, which is anti-inflammatory.

Spencer et al., (2017) remark IL-1B is released in a brain with low levels of PUFA. Fetal rodents, deficient in PUFAs during development of the CNS, had higher susceptibility to EAE (Clausen & Moller, 1967).

PUFAs attach to cannabinoids receptors, CB1/*CNR1* (brain) & CB2 (immune system). Spencer et al., (2017) remarked omega-3 fatty acids interact with the endocannabinoid system in the brain, improving depression. The authors also noted cognition, pre-dementia, and mood are affected by early-life stresses, and appropriate nutrition with PUFA, and polyphenols, along with the absence of significant stress and adversity in early life, are what makes for a healthy emotional brain in adulthood. Sources of PUFAs in the diet include chicken, pork, and nuts, such as walnuts, peanuts, and cashews.

Caruso et al., (2013) citing Gupta et al., (2012), conclude saturated fats, not unsaturated fatty acids, induced astrocytes to release inflammatory TNF-a and IL-6, which with TLR4 (which can be inhibited by *a-MSH*), and activated the innate immune system. A high saturated fat diet produces omega-6 vs omega-3 byproducts. The high fat diet which concerned Swank, increases circulation of saturated fatty acids and cytokines (Caruso et al., 2013; Spencer et al., 2017), and these cytokines produce a mild immune challenge. Saturated fatty acids reaching the hypothalamus showed an inflammatory response.

Dolan (2003) reviewed studies indicating the liver's antioxidant systems benefited from fish oil (Ruiz-Gutierrez et al., 1999) as well as did the course of MS (Simopoulos, 2002). Montesano (2012) hypothesized one lifestyle or dietary change the British air force may have brought to the Faroe Islands, (whose native population showed a spike in MS), were candy bars distributed by soldiers to the native population. The compositional fat used in production during the war was a source of omega 6, leading to ArAc, not omega-3 found in the native fish. The change in dietary fat, may have led to an epigenetic phenomenon, along with other changes to the environment, including toxins in the air by cigarettes and aircraft, or pets and pathogens.

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COMORBIDITIES IN MULTIPLE SCLEROSIS AND FAMILIAL CO-OCCURENCES (Table 1.)

Thyroid dysfunction and disease

MS does not often show as familial recurrence, however, there is an over presence of autoimmune conditions in families of the MS patient, and the largest contributor is autoimmune thyroid disease (Weiner 2004). Broadley et al. (2000), discovered high frequencies of autoimmune conditions in first-degree relatives of MS patients, with the highest association being Graves' thyroid disease. Sloka et al., (2005) also found a co-occurrence of Graves' disease in MS patients**.**

Seyle (1984) noted thyrotropic hormone (TTH) is stimulated during the stress response. Barres et al., (1993b) found thyroid hormone triiodothyronine (T3) is involved with oligodendrocyte differentiation. Rodriguez-Pena et al., (1993) found the start of myelination is delayed in rodents with hypothyroid and accelerated with hyperthyroid Marta et al., (1998) studied the effect of neonatal hyperthyroidism on rodent oligodendrocytes, and myelin. Evidence showed hyperthyroidism, at 70 days of age, produced a myelin deficit, correlated to a decrease in oligodendrocytes, and a MBP dysfunction. These authors concluded sustained levels of thyroid hormones increase oligodendrocyte apoptosis, as myelin begins to appear in the CNS about the same time as the thyroid gland becomes active. ***Thyroid hormone receptor interactor 13 (TRIP13)*** maps to 5p13.3, with the highest expressions in the testes and the lymph nodes, and interacts with thyroid hormone receptors, also known as hormone-dependent transcription factors. ***Inhibitory synaptic factor family member 2B (INSYN2B)*** maps to 5q35, with the highest expression in the corpus callosum of the brain, and in the tissues of the thyroid.

Graves' disease

Rioux & Abbas, (2005), associate locus 2q31-q35 to the genes for type II diabetes, and Grave's disease. Sloka et al., (2005) found a co-occurrence of Graves' disease with MS. Karabon et al., (2009) suggested dysregulated *CTLA4* expression in MS could result from variations in genetics, and these authors showed disease susceptibility was impacted by both membrane and cytoplasmic *CTLA4,* and perhaps disease progression is a result of an inadequate down-regulation of the T-cell response.

Non-insulin dependent diabetes mellitus, Type II

IDDM12/ Cytotoxic-T-Lymphocyte-Associated Antigen 4 (CTLA4) are mapped to 2q31-q35, the locus for non-insulin dependent diabetes. *CTLA4* is a costimulatory molecule in T-cell activation and is associated with diabetes and thyroid disorders (Martino et al., 2002). *CTLA4* is a suppressive marker for Treg cells (Danikowsi, Jayaraman, & Prabhakar, 2017).

Insulin-dependent diabetes mellitus, Type I

Insulin-dependent diabetes mellitus-18 (IDDM18) maps to 5q31.1-q33.1, is considered autoimmune, and like MS, has complex genetic and environmental contributors (Berholdt et al., 2004). In a Danish study, Nielsen et al., (2006), discovered co-occurrence of MS and type I diabetes within an individual, and to a lesser degree within a family. The concordance rate of *IDDM18* is about 30% **(**Stejskal & Stejskal, 1999**).**

Epilepsy, seizures and febrile seizures

Coulter & Steinhauser (2015) study of epilepsy revealed alterations in expression, localization, and function of astrocyte K^+ and water channels, or aquaporins (AQP). In addition, malfunction of GLU transporters, and astrocytic glutamine synthetase, which degrades glutamate to glutamine, has been observed in epileptic tissue. These findings suggest dysfunctional astrocytes are crucial players in epilepsy. At the synapses, astrocytes help control ions like K+ and neurotransmitters in the extracellular space (Barres 2008).

Leibowitz & Adler (1973) address findings of convulsions in MS were first described by Wilhelm von Leube in 1871**.** Eriksson, Ben-Menachem & Anderson, (2001) discovered epileptic seizures in MS occurred 7 times greater than in the general population, more frequent during the progressive course, and produced cognitive decline, by what appeared to be neuronal damage in later stages as of MS. Seizures, and lack of oxygen, kill neurons by the entry of excessive amounts of Ca2+ into the cell. The MS brain shows a significant deficit in oxygen, and Ge et al., (2013) concluded the underutilization of O2 might be the sign of MT dysfunction and neurodegeneration. Allen, Seminog & Goldacre, (2013) concluded strong evidence links MS and epilepsy, hypothesizing an underlying mechanism for both. Sponsler & Kendrick-Adey (2011) concluded there had to be a relationship between seizures and MS, because the prevalence of them was higher in MS than in the general population. Lund, et al., (2014) found in recent data the frequency of seizures in MS varies from 1.5% and 7.8%. Kavcic & Hofmann, (2017) found corticosteroids partly moderated the unprovoked, sporadic seizure susceptibility in MS.

Iwasaki et al., (2002) found ***familial febrile seizures (FEB4)*** mapped to 5q14-q15, may be the most common linkage in families with febrile seizures. Steinlein (2008) includes febrile seizures, those generated by fever in infancy and childhood, in his review of genetic associations with various types of epilepsy. Later in life, these benign seizures occurring in 2-4% of children, may increase for temporal lobe epilepsy. (Berg et al., 1999 cited in Dube, Brewster & Baram, 2009).

Fever

Hyperthermia, in animal models, causes secretion of IL-1B (*5q32*), which mediates fever (Dube, Brewster & Baram, 2009). Prostaglandins (PG) also raise body temperature, as well as LPS (Taylor, 2005). Fever can be caused by astrocytes, as they

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secrete inflammatory mediators (Hanada et al., 2009 cited in Caruso et al., 2013). Fever has shown to be reduced by injectable administration of *a-MSH*.

Generalized epilepsy with febrile seizures, plus, type 3 (GEFSP3) maps to 5q34, **and *generalized epilepsy with febrile seizures plus, type 7 (GEFSP7)*** maps to 2q24.3. **Gamma-aminobutyric acid, gamma 2 (GABRG2**) functions also as a histamine receptor, and mutation is correlated to childhood absence epilepsy and febrile convulsions (Kananura et al., 2002). **Gamma-aminobutyric acid type A receptor, beta 2, alpha 6, alpha 1 subunit (GABRB2, GABRBA6, GABRA1)** all map to 5q34. Genetic generalized epilepsy, which takes place in infancy is linked to GABA(A) receptor GABRG2 (Scheffer et al., 2009). GABRA1 is involved in juvenile myoclonic epilepsy (JME) (Steinlein, 2008).

Irritable bowel diseases: Crohn's and ulcerative colitis

Magyari et al., (2014) noted various autoimmune comorbidities in MS, including Crohn's, lupus and diabetes. **Inflammatory bowel disease (IBD5**)*, maps to 5q31. Giallourakis et al., (2003) discovered *IBD5* linked to the general risk for the inflammatory bowel conditions of Crohn's disease (CD) and ulcerative colitis (UC). Like MS, Crohn's has no single gene as its cause, and environmental factors play a large role. Rajora et al., (1997), discovered in the rodent model of IBD, the peptide *a-MSH* reduced fecal blood loss by over 80%, inhibited inflammation and NO release in lower bowel tissue, and inhibited weight loss. These authors also found the binding of *a-MSH* to the MC1R helped CNS disease and injury because of LPS. Scully (2014) suggested the antimicrobial properties in VIP, *a-MSH* and ghrelin, may be important in Crohn's disease, due to a noticeable imbalance between commensal, and pathogenic bacteria**.**

Gathungu et al., (2018) found *GM-CSF* (5q31) plays a critical role in maintaining the homeostasis of the intestines, and linked autoantibodies to *GM-CSF,* to the aggressiveness of the disease course in Crohn's. **Histamine Receptor (**HRH2)** maps to 5q35.2, and its ligand, histamine, is responsible for motility in the gastrointestinal tract, along with secretions of the intestines.

Parkinson's disease

Parkinson's (PD) was the first disease of the Industrial Revolution (Hatherill, 2003 cited in Montesano, 2012). One of the major dopamine tracts in the brain involves the "black" area known as the subtantia nigra. This area of the brain is black, due to the neuromelanin. In Parkinson's, the neuromelanin reduction in the substantia nigra and locus coeruleus, produces less DA, with a loss of neurons, and astrocytes. PD occurs less in the black skinned phenotype, suggesting a potential association of skin melanin and neuromelanin. Bohnen & Albin, (2011) reviewed the possibility the white matter lesions in PD that produce negative motor deficits, and cognitive deficits, both associated with the condition. Rocha et al., (2012) concluded that *GDNF (5p13*.2) from astrocytes is a major contributor to the control of microglial activation in Parkinson's

disease, suggesting a role in inhibition of neuroinflammation, hypothesized to kill 90% of DA neurons in the substantia nigra

Polio and post-polio syndrome

Poskanzer et al., (1963) observed epidemiologic similarities and patterns between the enteric virus for polio, and MS. A believf developed MS was caused by an enteric infection. Murray (1976) found an association between an outbreak of polio, and an unusual occurrence of MS cases in Colchester County, Nova Scotia. Pezeshkpour & Dalakas (1988) observed loss of motor neurons in polio, and pathology of reactive gliosis and suprising mild, to moderate, perivascular and brain tissue inflammation, extremely comparable to MS. Bruno et al., (1991; 1994) found the polio virus causes scarring of WM in certain areas of the brain. Lesions in the reticular formation produced the most severe fatigue, but the fatigue and pain, were not explained by the damage the virus had done to motor units. *GDNF* (5p13.2) prevents apoptosis of motor neurons by severing of the axon. Razavi et al., (2015) concluded *GDNF* also helps regenerate axons after spinal cord injury and prevents motor neuron degeneration in animal models of ALS.

Post-polio syndrome (PPS) fatigue develops 30+ years after the acute polio infection. Besides worsened fatigue, there is a slow progression of muscle weakness, a form of muscle atrophy (Dalakas et al., 1986), and the atrophy occurs in both muscles previously affected by the infection, and those spared. These authors found muscle strength declined 1% per year, and believed it was due to dysfunction in the motor neurons which had survived, as there was no way to demonstrate it was virally activated. The conclusion of these authors was post-poliomyelitis neuromuscular symptoms may be due to an undefined dysfunction in surviving motor neurons presenting with muscular atrophy, and the fatigue of PPS. Wyatt (2014) argued for a genetic susceptibility in polio, although making the association to one or more specific genes, consanguinity was a factor. This author suggested both paralytic polio, and overt tuberculosis, depended on individual genetic susceptibility.

Survival of motor neuron 1 and 2 (SMN1 & SMN2), map to 5q13.2, the gene for the survival of motor neurons. The highest level of expression occurs in the spinal cord and maintains the specialized motor neurons, also found in the brain stem. *SMN1 & SMN2* are involved with muscle weakness, atrophy and functional disability. Leibowitz & Adler (1973) found the main symptom of MS in the northern born black (negroe) populations was motor weakness. ***Heat shock protein family B (small) member 3 (HSPB3)*** is mapped to 5q11.2 and is muscle specific, as it is involved in neuromuscular disorders, which show degeneration of motor neurons in the anterior horn of the spinal cord, and clinically a muscular atrophy syndrome in the legs without sensory loss. This gene is associated with *CMTD* (5q23.1). ***Neuronal apoptosis inhibitory protein (NAIP),*** maps to 5q12.2-q13.3. Reyes and colleagues (2017) concluded this sensor of the homeostatic balance of immune cells performs a pro-inflammatory mechanism when interacting with

bacteria. It is thought *NAIP* is a modifier of spinal muscular atrophy caused by mutations in neighboring genes *SMN1 & SMN2*.

Tuberculosis

Leibowitz & Adler (1973) mentioned the "indirect" factor of malnutrition on tuberculosis, as a metaphor for the same type of factor in the pathogenesis of MS, and somehow, deaths from TB correlated to countries with MS. Anti-inflammatory *IL-2* is supported by the protein and nutrients derived from a diet rich in meat, fish and vegetables, not starches and sugar. Dolan's cluster study (2003), found statistical significance in the consumption of meat during developmental years until age 18 and association with a reduced risk of developing MS.

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, correlates to the frequency of MS. TB, as a non-brain antigen, was also discovered to cause axonal damage in the spinal cord, leading to myelin damage in guinea pigs (Wisnewski & Bloom 1975). Wikstrom (1975) studied the conditions of MS and TB in Vaasa, Finland, and concluded the highest rate of both conditions might reflect a common genetic factor. Higgins et al., (2008) showed rodents infected with *M. tuberculosis,* and deficient in *GM-CSF* (5q 31), had no ability to express an adequate Th1 response to kill the bacteria by phagocytosis performed by macrophages. NO is released from macrophages reacting to *M. tuberculosis.* Rock et al. (2005) found both microglia and astrocytes were infected by *M. tuberculosis,* and microglia were the principal cells infected, causing them to express proinflammatory cytokines and chemokines, which could be stopped by the application of steroids. Othman et al., (2018) concluded neurons infected with TB were more vulnerable to death by apoptosis than infected astrocytes, because the high levels of VEGF prevented the apoptosis of the astrocytes. ***Tyrosine kinase 4 receptor (FLT4), vascular endothelial growth factor receptor 3 (VEGFR3)*** map to 5q35**.** *FLT4* is the receptor for vascular endothelium growth factor (VEGF). This gene is involved with immunity, as in TB. The *VEGFR3* receptor maintains the lymphatic epithelium by binding VEGF. Mutation can lead to hereditary lymphedema by disrupting signaling in the small or absent tubes that carry lymph fluid. The clinical swelling of lymphedema appears to be a symptom of MS. This gene is thought to be involved in both formation of lymphatic vessels from pre-existing ones, and maintenance of the lymphatic endothelium of tissues such as adrenal glands, fat, spleen and lymph nodes.

Stamatovic et al., (2008) identify VEGF is a vasogenic agent, which can disturb the BBB, resulting in higher than normal permeability. A similar role applies to histamine, substance P, endothelin 1, and bradykinin. Growth factors including FGF, PDGF, VEGF and EGFR are also involved in hyper-permeability of the BBB. These authors state the most progressive breakdown of the BBB comes with inflammatory conditions of the CNS, no matter if it is primary or secondary. The edema of stroke and brain trauma disrupts the junctions. The endothelial junctions change and allowing for an increase of leukocyte traffic into the brain. Cytokines IL-1B, TNF-a, INF-y, chemokines, and matrix metalloproteinase (MMP2, MMP9) have a role of attracting the leukocytes.

Summers, Greisen, & Appel, (1979) observed the perivascular reaction, and inflammatory changes in the vessel wall of CDV, are identical to those seen in MS. Poser (1994) refers to this identical pathogenesis in his argument the primary change in the blood vessel wall, and alteration of the blood-brain barrier, is inflammation. Poser (1994) believed the first event in MS was a vascular event, and argued it was a primary change in blood vessel wall that led to the alteration of the BBB, and Poser (1997) claimed these alterations did not repair, leaving the BBB compromised. Transient opening of the BBB occurs during and after epileptic seizures. Barres (2008) highlighted the role of reactive astrocytes is to seal the BBB after brain injury (Bush et al., 1999 cited in Barres, 2008). The BBB is intact in the embryo at days eleven and twelve, when blood vessels enter the brain tissue in rodents (Saunders et al., 2008, cited in Barres, 2008). Postnatal, the astrocytes may maintain the function of the BBB (Cahoy et al, 2008, cited in Barres, 2008).

Schizophrenia

Schizophrenia susceptibility locus (SZD1) 5q11.2-13.3**,** shares the same locus as *CRHBP,* which inactivates CRH. Sherrington et al., (1988) studied seven British, and Icelandic, families with multiple members affected by schizophrenia, and concluded this single gene showed strong evidence for causation of the disorder. Macciardi et al., (1992) reported findings at 5q11.2-13.3 for schizophrenia in a northern Italian population. Paunio, et al., (2001) discovered Finnish families were susceptible to schizophrenia at locus 5q. There is also an association related to schizophrenia at 2q11.

Schizophrenia surfaces in adolescence, and is often a familial disorder, as 50% of children with schizophrenia have parents with it. Twin studies support a 50% genetic influence. Like MS, there are several hypotheses for its pathogenesis, including a role for MHC and T cell responses (Mokhtari & Lachman, 2016). These authors cite genome wide association studies for a strong genetic association between HLA locus and schizophrenia, and suggested infectious disease and or/ autoimmune processes lead to the development of schizophrenia. Mallya et al., (2017) concluded it remains unknown how genetic variability in a region near enhancers of B-cells leads to the disorder of schizophrenia

Arneth (2017) did a simultaneous review of MS and schizophrenia, and found notable similarities in the comparison, including the larger ventricles in the brain, indicating less neurons and glia. Sayo, Jennings & Van Horn (2011) confirmed ventricular enlargement is one of the greatest reported neurological biomarkers for schizophrenia. Makara-Studzinska & Los (2012) found both the schizophrenic, and their healthy siblings, showed enlarged third ventricle, temporal anomalies and irregularities within the frontal lobe, including lesions, but the healthy had less of the brain irregularities. Mallya, et al., (2018) describe neuropathological changes in schizophrenia to include ventricle size, as well as decreased dendritic spine density in the prefrontal cortex (PFC). These authors identify microglia, and perhaps astrocytes, as the glial cells involved in the synaptic

pruning during development through adolescence, and that microglia phagocytose the synapses (Spencer et al., (2017). Volterra, & Steinhauser, (2004) discuss the modulation glial cells have on synapse in the hippocampus.

The third ventricle lies close to the hypothalamus (Spencer et al., 2017). The neuroendocrine system in the cells of the hypothalamus are different from the conventional autonomic neurons, releasing hormonal secretions into the bloodstream, ex. pituitary-vasopressin (VIP) and anterior pituitary-tropic hormones. The posterior pituitary has leaky blood vessels that are not fenestrated, and an absent BBB to allow neurosecretory products to pass into circulation, such as NE, 5HT and melatonin. This leaky region is isolated from the rest of the brain by specialized ependymal cells called *tanycytes*, which line the surface of the third ventrical, and contact the CSF (Bolborea et al., 2013). *Tanycytes* are sensitive to glucose, and can respond to transmitters associated with arousal, and the drive to feed, and appear to be part of the hypothalamus, which controls body weight and energy balance. At least some *tanycytes* are stem cells and may be stimulated by diet to generate new neurons. Current research has looked at the improvement in MS through starvation methods, citing leptin in changing the immune response in EAE (Hoag, 2003).

Schizophrenia was uncommon prior to 1800, but rose rapidly in 1800s Europe, and the United States (Torrey & Miller, 2002). Like MS, schizophrenia presented highest in Ireland, Scandinavia (northern Swedes) and Eastern Europe (Croatia), and less in southern Europe. These children are more likely born in winter/spring, and many are vitamin D3 deficient. Fritzsche (2002) noted a "striking epidemiological overlap" between the sporadic schizophrenia, which expressed seasonally, and the seasonality of MS, revealing a striking epidemiological overlap between schizophrenia and MS.

Neuronal regeneration related protein (NREP) maps to 5q22.1 and appears to have a role in neural function and axonal regeneration. **Neurogenin 1 (NEUROG1)** maps to 5q31.1, as the gene for the transcriptional regulator that initiates neuronal differentiation. *NEUROG1* is associated with the neural crest, as well as embryonic stem cells. **Early Growth Response 1 (EGR1)** maps to 5q23-31. Sukhatme et al., (1988) studied *EGR1* for early growth response in fibroblasts, epithelial cells and lymphocytes. *EGR1* mRNA increases during cardiac and neural cell differentiation, but also in membrane depolarization of nerve cells, concluding *EGR1* may regulate transcription in diverse biological processes.

Dopamine link

The dopamine hypothesis is based on excessive dopamine in the synapses, and excessive DA receptors in various parts of the brain. **Glial cell derived neurotrophic factor (GDNF),** maps to 5p13.2 as a potent trophic factor secreted by astrocytes to control the development and survival of neuron, including DA neurons. Immune cells, T cells, B cells, and monocytes express *GDNF* (Vargas-Leal, et al., (2005).

T. gondii link

Prandovszky (2011) noted the parasite *Toxoplasmosis gondii* (*T. gondii*) found in cats, increased dopamine (DA), and potentially linked to the condition of schizophrenia. Burgdorf et al., (2019) recently concluded the causal relationship between *T. gondii* and schizophrenia.

Histamine link

Histamine Receptor (HRH2) maps to 5q35.2, and binidng histamine is responsible for motility in the gastrointestinal tract, along with secretions of the intestines. Histamine can disrupt the BBB acting as a vasogenic agent (Stamatovic et al., 2008), and mutations of this gene have been linked to schizophrenia (Deutsch et al., 1997).

D-serine link

D-serine is a neuroactive neurotransmitter secreted by astrocytes (Barres, 2008), and associated with schizophrenia, and helps in both this syndrome, depression and the cognitive issues involved with schizophrenia (Mackay et al., (2019). L-serine is the supplemental form used as a potential treatment for ALS.

POMC link

Miller et al., (1993) reviewed the dysregulation in auditory gating found in schizophrenics. *A-MSH* increases auditory gating, whereas MCH has the opposite effect. When MCH was administered prior to *a-MSH*, the ability of *a-MSH* to increase auditory gating was blocked, indicating the antagonistic relationship of the peptide.

Glutamate link

Glutamate is the brain's predominant excitatory neurotransmistter. Muller & Schwarz (2008) compared the opposite imbalance of glutamatergic neurotransmission in schizophrenia and major depression, claiming the secretions of activated microglia and astrocytes make additional glutamate contribution. Chen et al., (2010) reviewed the association with schizophrenia and bipolar disease. These authors discovered the neurotransmitter glutamate acts as an immunomodulator.

Alterations in glutamate homeostasis was found in the brains of those with MS (Geurts et al., 2005 cited in Klaver et al., 2013). Both epilepsy and MS show elevated glutamate in the CSF, from either glutamate signaling, uptake, and/or metabolism. The genes for two receptors of glutamate (GLU) occur at loci 5q33.2 *(GRIA1)* and 5q35.3 *(GRM6).* ***Glutamate receptor subunit 1/ionotropic receptor AMPA subunit (GRIA1)*** maps to 5q33.2 and is a subunit of the AMPA receptor for GLU. Moroni (1999) cited in Richard et al., (2009) specified tryptophan based kynurenic acid from the kynurenine pathway antagonizes the AMPA glutamate receptor.

Glutamate receptor (GLUR1) maps to 5q33.2, with response to glutamate activity, along with the regulation of postsynaptic cytosolic Ca2+ ion concentration. Lee et al., (2010) concluded this receptor might mediate synaptic plasticity, in addition to long-term potentiation, and depression, in the hippocampus, important for the enhancement of

emotional learning (Hu et al, 2007 in Lee et al., 2010). Hu et al., (2007), concluded NE phosphorylation of *GluR1* provides the molecular mechanism for emotional stress to enhance learning and memory. Hefferan et al., (2007) determined spastic animals express a significant increase in *GLuR1* in their lumbar spinal cord tissue, but a decreased expression GluR2 and GluR4. *GluR1* increase immunoreactivity in reactive astrocytes and reduction of spasticity and rigidity occurred as a result of down regulating this receptor on neurons and astrocytes in the lumbar spinal cord. Relaxation of skeletal muscles is achieved by inhibiting the excitatory motor neurons in the spinal cord. **Glutamate receptor metabotropic, 6 (GRM6)** mapped to 5q35.3, is an additional locus for L-glutamate, connects with night blindness.

Stroke

Krushkal et al., (1998) identified the human chromosomal region of the long arm of chromosome 5, which contains the loci for *ADRAB2*, *ADRA1B*, and *DRD1A* as the important genes in systolic blood pressure regulation. **Susceptibility to stroke (STRK1),** maps to 5q12, and is linked to ischemic stroke in Caucasians (Nakayama et al., 2007). In cerebral ischemia, inflammatory cytokines can be reduced by application of *a-MSH*, which reduces both iNOS and COX2 gene expression in the hypothalamus and in astrocytes (Rajora et al., 1997; Carniglia et al., 2013). Savos et al., (2010) investigated the immunomodulatory role of *a-MSH* to modulate the Th1 response to myelin basic protein (MBP) following a stroke in which a cerebral artery was occluded. Medvedeva (2014) worked with the neuroprotective peptide SEMAX for strokes, and found this fragment of ACTH promoted neurons survival from hypoxia and glutamate neurotoxicity. SEMAX influences the expression of the genes that form the vascular system, its functioning, inhibits NO synthesis, and acts on microglia and immune system cells which have APC potential, such as leukocytes and dendritic cells.

Cancer and leukemia

Wolfgram (1975) reviewed 83 diseases and reported a unique and peculiar similarity between the geographical distribution of MS and colon cancer. **Mutated in colorectal cancers (MCC),** maps to 5q22.2, and is involved with tumor suppression and related to colorectal cancers. The locus 5q23 is associated to cancers, including **glioma and astrocytoma.** Behan, Chaudhuri & Roep (2002) identified malignant glioma/astrocytoma are associated with MS. The gene **TNF alpha induced protein 8 (TNFAIP8)** maps to 5q23.1 as one of the family of tumor necrosis factor (TNF), and is associated with carcinogenesis (Lou & Liu, 2011), acts as a negative mediator of apoptosis and may play a role in tumor progression. Garcia et al., (2015) concluded both human, and canine, mammary tumor cells should be investigated for the use of canine distemper virus (CDV) as an oncolytic viral therapy, because of the expression of TNFAIP8 in the cell line. **Thyroid hormone receptor interactor 13 (TRIP13)** maps to 5p13.3, with the highest expressions in the testes and the lymph nodes, and interacts with thyroid hormone receptors, also known as hormone-dependent transcription factors. *TRIP13* is also involved in lung cancer. Deletions of 5q are related to malignant

myeloid cancers, and suggest genes located at 5q may function as leukemia suppressor genes (Le Beau, 1992), while 5q31.1 was deleted in patients with malignant myeloid disorders.

Wang et al., (1997) noted loss at this locus might be involved in the pathogenesis of malignant myeloid disorders. **Familial Adenomatous Polyposis (APC)** is mapped to 5q22 and is a form of colon cancer. **Growth GDNF family receptor alpha 3 (GFRA3)** is mapped to 5q31.2, binds with *GDNF*, and artemin (ARTN), another neurotrophic factor, found in many tissues, and highest in the colon and testes. ARTN also acts as a cancer stem cell in breast cancers (Ding et al., 2014). Adjacent to this locus are proteins for *IL3, IL4, IL5, IL9,* and *CSF-2.*

Cardiac conditions

Mincu et al., (2018) studied MS patients with decreased left ventricular (LV) systolic function, right ventricular function, LV diastolic and left atrial (LA) function, and concluded impaired biventricular function, with normal endothelial and arterial function. Androdias et al., (2017) reported there are rare cases of Takotsubo cardiomyopathy in MS relapses, where the left ventricle is weakened, and results from severe emotional, or physical, stress-death of a loved one, serious accident, sudden illness, or natural disaster, with the main symptoms are chest pain and shortness of breath*.* **Atrial Septal Defect with or without atrioventricular conduction defects (ASD7***)* maps to 5q33.3, and relates to atrial fibrillation (AFib), an irregular heartbeat, which may cause blood clots, stroke, heart failure, and other complications of the heart.

Systemic lupus erythematosus (SLE)

Jacome-Sanchez, et al., (2018), report a case of a patient in Equador where MS and **SLE** (5q21-23) coexisted. Equador consistently shows a low prevalence of MS.

Charcot-Marie Tooth disease

Charcot-Marie Tooth (CMTND), is a demyelinating condition, and maps to 5q23.1 in the Algerian population, as the second locus for this condition (Le Guern et al., 1996; Kessali et al., (1997). Behan, Chaudhuri & Roep (2002) treated a patient who had **CMTND** as a comorbidity to MS.

CONCLUSION

In conclusion, this review suggest new information that susceptibility to MS stems from a genetic condition brought about by a multitude of potential pathways, suggesting dysregulation along chromosomes 2 and 5, especially a cluster of genes at loci 5q31-q33. The inclusion of multitudes of neighboring specific genes from chromosomes 2 and 5, points to an integrated, yet complicated genetic susceptibility. The various categories of proteins identified from online gene resources, concludes the pathway to the disorder of MS is relevant to multiple medical disciplines treating symptoms of body, and mind. There may be no single specialization which can hold complete responsibility, if this theory is correct that MS is the dysfunction of a unified system of loci on chromosome 2, and 5, heritable from other generational health conditions associated with the same chromosomes, and triggered by a plethora of environmental causes, resulting in destruction of white and gray matter of the CNS.

There are approximately 844 confirmed genes on chromosome 5, which comprises 6% of a human's DNA. Ebers et al., (1996) searched the entire genome in MS, and mentioned 5p as a locus for multiple sclerosis. Hilde et al., (2005) mapped 5p14-p12 to MS from evidence of genetic epidemiologic heritable susceptibility for MS in Finnish families. Among the MS-associated risk loci in the *Genetic Atlas of Multiple Sclerosis* by Didonna & Oksenberg (2017), 5p13.2 was identified because of an association to IL-7R. Ban et al., (2002) found possibly linkage at 5q11-21 for Australian siblings who both developed MS. Chromosome 2 is the second largest chromosome and represents 8% of total DNA in cells. Ban et al., (2002) found possibly linkage at 2p13 for Australian siblings both having MS.

POMC, and its cleavage to MSH, ACTH, B-endorphin, should be further addressed with as much weight as cortisol, and catecholamines, in the role of the stress response in MS, as a-MSH has an anti-inflammatory and anti-cytokine role, and scarring astrocytes express the MC4R. The genes on chromosome 5 related to glucocorticoids and specific G-protein coupled receptors present pathways for the multiple symptoms that result from the cascade of stress, including pain, bladder control, cognitive functioning and emotional changes. Over two hundred years ago, Jean-Martin Charcot speculated grief and adverse social conditions were related to the onset of MS, and within this new perspective, there may be some validation for Charcot's theory. Chromosome 5, specifically, appears to be the model for neuropeptides and their receptors, joining brain, glands, and immune system in a network of communication based on the biochemistry of stress and emotions (Pert et al., 1986).

TABLE 1.

Chromosome	Genes
2	STAT4, IL1A, *POMC*, TPH2, GEFSP7, IDDM12, *CTLA4*, *MSH2*, *MSH6*
5	FAXDC2, ADRA1B, FGF1, GPR151, GRK6, *IDDM18*, APC, *SCZD1*, *HSP70*, *STRK1*, GDNF, *TNFAIP8*, LIFR, C9, *ADAM19*, ADRAB2, GR1A1, *DAT1 DRD1A*, PTGER4, LY64, IRF1,CD74, IL13, ITK, IL12B, IL7R, LECT2, CD14, IGES, IG1P, IK, HMHB1, IL17B, PDGFRB,CAMK4, HTR4, NAIP, GCCR, *GRL*, CRHBP, TIMD4, TIM3, PMCH1, PMCHL2, MRPL36, NDUFS6, NDUFS4, CKMT2, COX7C, GPX8, GPX3, NREP, NRG2, *HTR1A*, PCDH-12-PGDHGC5, FGF18, GABRP, *GABAA*, HCN1, VLGR1, VEGFR3, CF2R, F12, F2RL2, GEFSP3*, ASD7, IBD5, FEB4, GM-CSF, IL5, IL6ST,CSF2,CSF1R, DCANP1, INSYN2B, CPHD2, TPH2, GLUR1, GR1A1,GABRG2, GABRBA6, GABRA, MSH3*

Genes associated with multiple sclerosis, comorbidities, and *familial* co- occurrence of diseases and disorders.

ABBREVIATIONS

Ach Acetylcholine

ACTH Adrenocorticotropic hormone

AD Alzheimer's disease

ADD Attention deficit disorder

AGRP Agouti related peptide

ALS Amyotrophic lateral sclerosis

AQP Aquaporin

APC Antigen presenting cell

ArAc Arachidonic acid

ATP Adenosine triphosphate

BBB Blood brain barrier

BD Bipolar disorder

cAMP Cyclic adenosine monophosphate

Ca2+ Calcium

CA Carbonic anhydrase

CDV Canine distemper virus

CMTND Charcot Marie Tooth disease

CNS Central nervous system

CO Carbon monoxide

CO2 Carbon dioxide

COX (1 & 2) Cyclooxygenase

CRH Corticotropin-releasing hormone

CSF Cerebrospinal fluid

DA Dopamine

EAE Experimental autoimmune encephalomyelitis

EBV Epstein Barr virus

EPI Epinephrine

5HT Serotonin

FGF Fibroblast growth factor

FSH Follicle stimulating hormone

GABA Gamma-Aminobutyric acid

GH Growth hormone

GLU Glutamate

GPCR G-protein coupled receptor

GSH Glutathione

GM Gray matter

HLA Human leukocyte antigen

HPA Hypothalamus-pituitary-adrenal

IBD Irritable bowel disease

IBS Irritable bowel syndrome

IDDM1 Insulin dependent diabetes mellitus

IDDM2 Non-insulin dependent diabetes mellitus

IFNy Interferon gamma

K+ Potassium

LH Luteinizing hormone

LA Left atrial

LPS Lipopolysaccharides

LV Left ventricular

LT leukotriene

MCH Melanocyte-concentrating hormone

MHC Major Histocompatibility complex

MMP Matrix metalloproteinase

mRNA Messenger ribonucleic acid

MS Multiple sclerosis

MSH Melanocyte-stimulating hormone

MT Mitochondria

Na+ Sodium

NAC N-acetyl cysteine

NADH Nicotinamide adenine dinucleotide

NAGM Normal appearing grey matter

NAWM Normal appearing white matter

NE Norepinephrine

NO Nitric oxide

PUFA Polyunsaturated fatty acids

PD Parkinson's disease

PFC Prefrontal cortex

PG Prostaglandin

PPS Post-polio syndrome

RA Rheumatoid arthritis

RBC Red blood cell

RNS Reactive nitrogen species

ROS Reactive oxygen species

SLE Systemic lupus erythematosus

SNP Single nucleotide polymorphisms

SOD Superoxide dismutase

SZD Schizophrenia

TB Tuberculosis

TSH Thyroid-stimulating hormone

UC Ulcerative colitis

UVR Ultraviolet radiation

WM White matter

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