Supplementary File 1

Gene selection strategy

This supplementary file provides a short outline of the reasoning behind the inclusion of each gene, divided into the mechanistic subclasses that the genes are associated with. The sections outline how each gene is associated with multiple chemical sensitivity (MCS), other functional somatic disorders and/or the relevant pathophysiological mechanisms discussed.

Immune regulation:

Cytokines: Based on recent findings of abnormal immunological mediator levels in blood plasma from MCS subject, a panel of pro-inflammatory cytokines was included encompassing interleukin (IL)-1β, IL-2, IL-6, IL-8; IL-10 and tumour necrosis factor (TNF)-α,[1-5].

NFKB1: The Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (NFKB1) gene encodes a subpart of the important transcription factor (nuclear factor kappa-light-chain-enhancer of activated B cell) that are involved in cell survival and immune regulation,[6]. Upon activation, NF-κB can induce transcription of a number of MCS associated genes including the inflammatory genes (IL-1β, IL-6, TNF-α and IL-8), ceramide, inducible nitric oxide synthase as well as growth factors such as nerve growth factor and brain-derived neurotrophic factor) (BDNF),[7,8].

NOS2: Nitric oxide synthase 2, inducible (NOS2) encoded as nitric oxide synthase that can be induced by elevated levels of circulation cytokines. A recent study identified increased levels of nitic oxides and cytokines in blood samples from MCS subjects and increased NOS2 activation might be implicated in the observed higher levels of oxidative species,[2].

Sensory ion channel receptors:

Purinergic receptor: Purinergic receptor P2X, ligand-gated ion channel, 4 (P2X4) and purinergic receptor P2X, ligand-gated ion channel, 5 (P2X5) are both playing a sensory role in neuropathic, inflammatory pain and muscular fatigue and also serves as co-regulators of BDNF,[4,9-11]. P2X4 gene expression has also been reported upregulated in fibromyalgia (FM) patients and both P2X4 and P2X5 genes showed likewise higher expression rates in chronic fatigue syndrome (CFS) patients upon a symptoms eliciting exercise session,[5,12].

TRP receptors: Three members of the transient receptor potential (TRP) were included in the study i.e. TRP cation channel, subfamily V, member 1 (TPRV1), TRP cation channel, subfamily V,

member 4 (TPRV4) and TRP cation channel, subfamily A, member 1 (TRPA1). All three receptors are found on membranes of nociceptive, parasympathetic and sympathetic nerves as well as a on a variety of non-neuronal cells in most parts of the body, including the airways. Depending on the nature of the receptor, they can be activated by physical, chemical, and hormonal stimuli of both exogenous and endogenous origin,[13,14]. The included TRP receptors have been linked to airway and neurogenic inflammation and altered pain sensation in general,[14-17] and discussed as a factor in experimentally observed sensory hyper-reactivity and central sensitization in MCS subjects via altered nociceptive pain procession,[18,19].

GRIK2: Glutamate receptor, ionotropic, kinase 2 (GRIK2) is involved in circadian rhythm regulation and has been found associated with chronic fatigue syndrome (CFS) via specific genomic risk alleles and gene expression measured. A similar associated with MCS is thereof plausible,[20].

NMDA: The N-methyl-D-aspartate receptor (NMDA) is represented by the glutamate receptor, ionotropic, N-methyl D-aspartate 1 (GRIN1) gene because GRIN1 an important subunit of the NMDA receptor. Increased NMDA receptor activity is an important component in central sensitization and the NMDA receptor has been suggested as a key component in the pathogenesis of MCS, CFS and FM,[21-23].

Serotonin receptors:

Serotonin receptor : Hypersensitivity of serotoninergic system have been linked to musculoskeletal pain in FM and genetic association studies have linked specific variations of the serotonin receptor 1A (HTR1A) and 2A (HTR2A) genes with chronic widespread pain as well as with the extent of pain experienced,[24], the number of somatic symptoms, the levels of fatigue experienced,[25,26] and with the risk of developing CFS,[26].

Adrenergic receptors:

The adrenergic receptors are associated with the "fight-or-flight" stress response in humans upon activations by catecholamines such as dopamine or adrenaline. Activation of these receptors can affect the activity of the sympathetic nervous system that regulates physiological factors such as contractile force, heart rate and blood flow. We included the two β-1 and β-2 adrenergic receptors that both have been found to have increased gene transcription rates paralleled with symptoms elicitation in CFS and FM,[4,5,12]. In addition, the catechol-O-methyltransferase (COMT) gene was included due to its proteolytic capacity toward catecholamines, thereby regulating the

activation pressure on adrenergic receptors. Increased COMT gene expression levels were likewise found increased in CFS patients after experimentally provoked symptom elicitation,[4].

Antioxidative enzyme:

Catalase: Catalase is a major regulator of intracellular hydrogen peroxide homeostasis in mammalian cells protecting the cell against oxidative damage. A study using blood samples from MCS subjects found significantly reduced capacity of the cells to degrade hydrogen peroxide and increased oxidative stress have often be mentioned in models of MCS,[2,2,21,27].

Growth factor:

BDNF: BDNF is involved in neuronal survival and synaptic plasticity of both the central and peripheral nervous systems, and increased level of BDNF has been associated with pain hypersensitivity, one of the shared symptoms of MCS, FM and CFS. Moreover, abnormal peripheral blood levels of BDNF have been reported in both FM and CFS patient,[28,29].

Substance P receptor:

The substance P receptor is a neuromodulator linked to neurogenic inflammation and is involved in regulation of symptoms such as mood, stress, pain, anxiety and neurotoxicity all symptoms shared between MCS, CFS and FM,[30-32]. In 2004, Kimata (2004) reported increased levels of circulation substance P in MCS subjects upon a volatile organic compound (VOC) exposure provocation,[33]. In this study, Substance P expression levels was monitored by quantifying mRNA levels of its membrane bound receptor, the Tachykinin receptor 1, known to be expressed by white blood cells,[30].

Sphingosine-1-phosphate pathway:

The sphingosine-1-phosphate pathway plays an important role in peripheral and central pain sensitization, which is symptom complexes that are characteristic for MCS as well as for FM, CFS and functional somatic disorder in general. Mediators of the pathway are likewise involved in regulation of T-cell migration, which is important for normal immunological regulation including cytokine release, those relevant for MCS pathogenesis. The pathway is highly sensitive toward physiological stress induction via multiple stress signalling pathways, and it is plausible that

imbalance of the pathway can constitute a component in MCS,[34,35]. The pathway was represented by N-acylsphingosine amidohydrolase (acid ceramidase) 1, sphingosine kinase 1 and sphingosine-1-phosphate lyase 1.

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