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Increased prevalence of two mitochondrial DNA polymorphisms in functional disease: Are we describing different parts of an energy-depleted elephant?☆

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ABSTRACT

About 20% of the population suffers from "functional syndromes". Since these syndromes overlap greatly in terms of co-morbidity, pathophysiology (including aberrant autonomic activity) and treatment responses, common predisposing genetic factors have been postulated. We had previously showed that two common mitochondrial DNA (mtDNA) polymorphisms at positions 16519 and 3010 are statistically associated with the functional syndromes of migraine, cyclic vomiting syndrome and non-specific abdominal pain. Herein, among individuals with mtDNA haplogroup H (HgH), the presence of these two mtDNA polymorphisms were ascertained in additional functional syndromes: chronic fatigue syndrome, complex regional pain syndrome, sudden infant death syndrome, and major depressive disorder. Polymorphic prevalence rates were compared between disease and control groups, and within each disease group in participants with and without specific clinical findings.
In all four conditions, one or both of the polymorphisms was significantly associated with the respective condition and/or co-morbid functional symptomatology. Thus, we conclude that these two mtDNA polymorphisms likely modify risk for the development of multiple functional syndromes, likely constituting a proportion of the postulated common genetic factor, at least among individuals with HgH. Pathophysiology likely involves broad effects on the autonomic nervous system.

1. Introduction

"Functional" symptoms, including pain, nausea, and fatigue, constitute the primary reason as to why individuals seek professional help with "physical" and "mental" health care providers. The cause is unexplained in at least a third of cases (Kroenke and Rosmalen, 2006). Prominent functional symptoms are often assigned to syndromes based on symptom clusters guided by expert consensus criteria. Some functional syndromes are common with a lifetime prevalence >10%, e.g. migraine and irritable bowel syndrome (IBS), while others are uncommon or rare but can result in severe disability, e.g. chronic fatigue syndrome (CFS), cyclic vomiting syndrome (CVS), and complex regional pain syndrome (CRPS).

Co-occurrence among the functional syndromes (Henningsen et al., 2007) is well established, for example, 67% of CFS patients have been reported to also have migraine (Peres et al., 2002) and 51% to have IBS (Whitehead et al., 2002). One study demonstrated an odds ratio for familial aggregation of 2.5 among multiple functional syndromes, and that the risk for different functional syndromes extended to the relatives (Hudson et al., 2003). High syndrome overlap among individuals and within families suggest the presence of common genetic factors

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(Hudson et al., 2003). In support of this concept is the broad spectrum of some therapeutic agents, such as amitriptyline, against multiple functional syndromes (Henningsen et al., 2007; Joshi et al., 2009; Rahimi et al., 2009; Smitherman et al., 2011). Could it be that the splitting of "functional" disease into different syndromes, often defined by divisions among medical sub-specialties, makes us into "blind doctors" describing different parts of the proverbial "elephant" (Fig. 1)?

Two potential uniting principles in functional disease are the autonomic nervous system and energy metabolism. *Aberrant autonomic function* (dysautonomia) has been documented in migraine (Daas et al., 2009), IBS (Pellissier et al., 2010), CFS (Hoad et al., 2008), CVS (Chelimsky and Chelimsky, 2007), CRPS (Riedl et al., 2001), and SIDS (Weese-Mayer et al., 2008), thus an effect on autonomic pathways is a plausible mechanism of action of a common genetic factor. *Aberrant energy metabolism* (mitochondrial dysfunction) has been demonstrated in migraine (Sparaco et al., 2006), CRPS (Higashimoto et al., 2008), CFS (Myhill et al., 2009), CVS (Boles and Williams, 1999), and SIDS (Läer et al., 2014). Maternal inheritance has been reported in migraine (Burnett et al., 2005), CVS (Boles et al., 2005), depression (Bergemann and Boles, 2010), IBS (van Tilburg et al., 2014), and SIDS (Beal and Blundell, 1988), suggesting that some of the common genetic factors in functional disease may be encoded on the maternally-inherited, cytoplasmic-located mitochondrial DNA (mtDNA). Full mtDNA genomic sequencing revealed highly statistically-significant associations with the common polymorphisms 16519T and 3010A among child-onset cases with CVS (Zaki et al., 2009). The same two mtDNA polymorphisms were highly statistically associated with migraine in adults presenting to two headache clinics (Zaki et al., 2009). The effects of these polymorphisms are great, as the data predict 11% prevalence of migraine in individuals with 16519C, 28% prevalence in individuals with 16519T, and 74% prevalence in individuals with both 16519T and 3010A. Adults with IBS whose pedigrees demonstrated probable maternal inheritance were significantly more likely to have 16519T than controls (odds ratio (OR) 5.8; 95% CI 1.5–23.1) or IBS without maternal inheritance (OR 5.2; van Tilburg et al., 2014). Furthermore, 3010A and/or the common mtDNA polymorphism 7028T were found to be statistically associated with IBS, non-specific abdominal pain, and the physiological/autonomic processes of gastric motility, satiation and rectal sensation (Camilleri et al., 2009). Recently, SIDS was found to be associated with 16519T (Läer et al., 2014).

The aim of this study was to determine if mtDNA sequence variation at 16519 and 3010 are associated with the additional functional and dysautonomia-related syndromes of CFS and CRPS, and thus may underlie some of the shared genetic component of functional/dysautonomic syndromes in general. We also tested major depressive disorder (MDD) in which migraine and IBS, conditions linked to dysautonomia, commonly occur (Breslau et al., 2003; Gros et al., 2009). Although comorbidity data cannot be ascertained due to early mortality, we also included sudden infant death syndrome (SIDS), which can be considered as a lethal dysautonomia (Weese-Mayer et al., 2008).

2. Methods

2.1. Participants

2.1.1. Chronic fatigue syndrome (CFS)

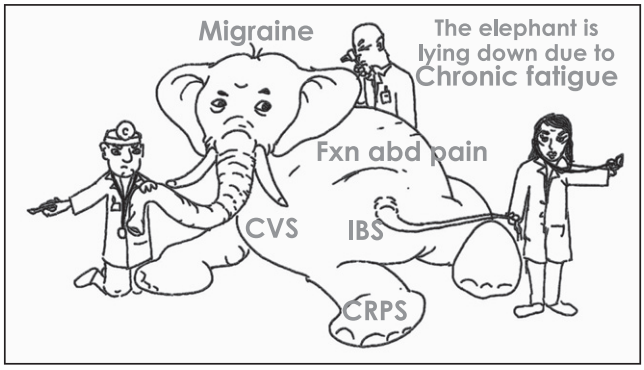
CFS patients consisted of adults (18–65 years of age) recruited from the United Kingdom or USA as previously reported (Zhang et al., 2010). All were given a clinical diagnosis of CFS based upon the 1994 Centers of Disease Control (CDC) criteria (Fukuda et al., 1994). Participants were administered various questionnaires (SPHERE, SF-36, McGill pain questionnaire, Pittsburgh sleep quality index and Chalder fatigue scale) which determine the presence of particular functional and dysautonomic-related symptoms and their severity (Zhang et al., 2010). A total of 162 participants met the above criteria and underwent mtDNA haplogrouping as described below.

2.1.2. Complex regional pain syndrome (CRPS)

Participants consisted of adults recruited throughout the USA and Canada who answered a study advertisement distributed by the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA) and American RSDHope. All had a prior practitioner-given clinical diagnosis of CRPS type I (formally known as reflex sympathetic dystrophy), which was verified by an on-line investigator-created survey with questions paralleling the International Association for the Study of Pain (IASP) consensus conference criteria (Merskey and Bogduk, 1994). The survey also queried regarding co-morbid functional/dysautonomic symptoms (Boles et al., 2009). A total of 140 participants met the above criteria and underwent mtDNA haplogrouping.

2.1.3. Sudden infant death syndrome (SIDS)

Participants consisted of infants who succumbed between two weeks to a year of age in the State of Maryland who were given the diagnosis of "SIDS" by a pathologist following standard clinical procedures, including an autopsy, as previously reported (Boles et al., 1998). Cases identified with a definable cause of death such as infection, abuse, or probable specific fatty acid oxidation disorders were excluded (Boles et al., 1998). A total of 313 participants met the above criteria, and those Caucasian infants in whom adequate tissue was available underwent mtDNA haplogrouping. SIDS was further divided into two sub-groups (Boles and Rinaldo, 2006), based on the concentration of hepatic free-glucose as measured by gas chromatography: a glucose-depleted (<1.2 μmol glucose per mg non-collagen protein) sub-group consisting of 20% of the cases in the larger study (Boles et al., 1998), and a glucose-normal sub-group comprising the remainder. This distinction was made based on the prior hypothesis that glucose depletion is a marker for a metabolic disorder or mitochondrial dysfunction.



CVS = cyclic vomiting syndrome, Fxn abd pain = functional abdominal pain (a common pediatric functional syndrome), IBS = irritable bowel syndrome, CRPS = complex regional pain syndrome

Fig. 1. The Functional Disease Elephant. CVS = cyclic vomiting syndrome, Fxn abd pain = functional abdominal pain (a common pediatric functional syndrome), IBS = irritable bowel syndrome, CRPS = complex regional pain syndrome.