Association of mitochondrial DNA in peripheral blood with depression, anxiety and stress- and adjustment disorders in primary health care patients

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Abstract
Mitochondrial dysfunction may result in a variety of diseases. The objectives here were to examine possible differences in mtDNA copy number between healthy controls and patients with depression, anxiety or stress- and adjustment disorders; the association between mtDNA copy number and disease severity at baseline; and the association between mtDNA copy number and response after an 8-week treatment (mindfulness, cognitive based therapy). A total of 179 patients in primary health care (age 20-64 years) with depression, anxiety and stress- and adjustment disorders, and 320 healthy controls (aged 19-70 years) were included in the study. Relative mtDNA copy number was measured using quantitative real-time PCR on peripheral blood samples. We found that the mean mtDNA copy number was significantly higher in patients compared to controls (84.9 vs 75.9, p<0.0001) at baseline. The difference in mtDNA copy number between patients and controls remained significant after controlling for age and sex (β=8.13, p<0.0001; linear regression analysis). The mtDNA copy number was significantly associated with Patient Health Questionnaire (PHQ-9) scores (β=0.57, p=0.02) at baseline. After treatment, the change in mtDNA copy number was significantly associated with the treatment response, i.e., change in Hospital Anxiety and Depression Scale (HADS-D) and PHQ-9 scores (β=1.00, p=0.03 and β=0.65, p=0.04, respectively), after controlling for baseline scores, age, sex, BMI, smoking status, alcohol drinking and medication. Our findings show that mtDNA copy number is associated with symptoms of depression, anxiety and stress- and adjustment disorders and treatment response in these disorders.

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1. Introduction

Mitochondria are ubiquitous organelles found in the cytosol of eukaryotic cells that process glycolysis and lipolysis products to generate the cellular energy carrier ATP, via oxidative phosphorylation (Hock and Kralli, 2009; Johannsen and Ravussin, 2009; Scheffler, 2001). In addition, mitochondria are also involved in cell apoptosis, proliferation and differentiation (Johannsen and Ravussin, 2009; Kasahara and Scorrano, 2014; Wallace, 2008). Mitochondria are essential for maintaining fundamental cellular processes in the organism. Therefore, mitochondrial dysfunction may result in a variety of diseases (Malik and Czajka, 2013; Michel et al., 2012).

The number of mitochondria per cell differs widely among different cell types, depending on the energetic requirements of the cells; e.g., there can be up to 2000 of mitochondria in liver cells (Bruce Alberts et al., 1994). Each mitochondrion contains between two and 10 copies of mitochondrial DNA (mtDNA) (Clay Montier et al., 2009; Legros et al., 2004; Robin and Wong, 1988). The mtDNA is a double-stranded, closed circular molecule encoding 37 genes essential for normal mitochondrial functioning (Campbell et al., 2012). One way to measure mtDNA content in a cell is to measure the mitochondrial to nuclear genome ratio, termed Mt/N and also called relative mtDNA copy number (Malik and Czajka, 2013; Malik et al., 2009). mtDNA copy number is specific to tissue type and to developmental stage and has been proposed as a marker of DNA damage and oxidative stress. The increase in mtDNA copy number is the early molecular events of human cells in response to endogenous or exogenous oxidative stress through cell-cycle arrest (Lee and Wei, 2005; Lee et al., 2000; Liu et al., 2003; Jeng et al., 2008). How mtDNA copy number is regulated remains unknown (Clay Montier et al., 2009). Altered mtDNA copy number has been shown to be associated with different types of diseases, such as cardiovascular diseases, diabetes, multiple sclerosis and various forms of cancers (Blokhin et al., 2008; Cheu-Feng Lin et al., 2014; Chen et al., 2014, 2015b; Lee et al., 1998; Lemnrau et al., 2015; Sun et al., 2015; Zhou et al., 2014).

Depressive disorders, anxiety disorders, stress- and adjustment disorders are common psychiatric disorders, with an estimated prevalence rate that vary between 12% and 32% of the total medical practice consultations in primary health care (Nordstrom and Bodlund, 2008; Vazquez-Barquero et al., 1997). These illnesses are associated with poor quality of life, reduced life expectancy, and places a large economic burden on society. Depression and anxiety are associated with excess mortality risk but the mechanisms remain obscure (Cuijpers and Smit, 2002; Penninx et al., 1999). Although the pathophysiology of depression has multiple facets, chronic life stress is known to have a role in the etiology of depression (Hammen, 2005; Liu and Alloy, 2010). Previous studies have investigated the relation between alteration of mtDNA copy number and psychiatric disorders including major depressive disorders (MDD), bipolar disorders, post-traumatic stress disorder (PTSD) and autism (Bersani et al., 2016; Cai et al., 2015a; Chen et al., 2015a; de Sousa et al., 2014; Yoo et al., 2017). However, the results are inconsistent (Cai et al., 2015a; Chang et al., 2014; Giulivi et al., 2010; He et al., 2014; Kim et al., 2011). Cai et al. reported an increased mtDNA copy number in MDD patients and in mice undergoing stressful exposures (Cai et al., 2015a). Whereas, He et al. did not find any association between mtDNA copy number and MDD (He et al., 2014). It is important to explore the association between mtDNA copy number not only in MDD but also in mild and moderate depressive disorders, anxiety, and stress- and adjustment related disorders as these disorders are much more common and knowledge about underlying mechanisms of these disorders, may lead to better preventive strategies in the future. To the best of our knowledge, however, only one study, which was performed by Kim et al. (2011) in elderly women, included both moderate and severe depression.

Moreover, most previous studies measured mtDNA copy number at a single time point, and only one study also examined the changes in mtDNA copy number after treatment. The authors of that study examined the potential changes in mtDNA copy number after treatment of MDD patients over an 8-week period (Nicod et al., 2015) and found that there is an association between mtDNA copy number and MDD, but no significant correlation between mtDNA copy number and the Hamilton Depression Rating Scale at different time points.

The present uses data from a randomized controlled trial (RCT) conducted by our group where we included patients with depression, anxiety and stress- and adjustment disorders from 16 primary health care centers in order to compare the effects of an 8-week mindfulness-based group therapy with treatment as usual (mostly individual-based cognitive behavioral therapy, CBT) on psychiatric symptoms (Sundquist et al., 2015). However, the biological effects of these treatments have not been fully investigated. In the present analysis, we used data on mtDNA copy number collected in the RCT at baseline and after the 8-week treatment. The first aim was to examine possible differences in mtDNA copy number between healthy controls and patients with depression, anxiety or stress- and adjustment disorders. The second aim was to examine the associations between mtDNA copy number and disease severity at baseline by self-rated scales and the third aim was to examine the association between mtDNA copy number and response after the 8-week treatment.

2. Experimental procedures

2.1. Study population

A total of 179 patients (ages 20-64 years) with depressive, anxiety and stress- and adjustments disorders were included in the present study. The patients were originally recruited from 16 primary health care centers in a randomized controlled trial (RCT) comparing mindfulness-based group therapy with TAU. The RCT included a group of patients with depression, anxiety or stress- and adjustment disorder (Sundquist et al., 2015). Patients were recruited between Jan 4, 2012 and March 22, 2012 from 16 primary health centers in urban and rural settings in the region of Skåne, southern Sweden. The inclusion criteria were as follows: one or more of the following ICD-10 psychiatric diagnoses: F32.0, mild depressive episode; F32.1, moderate depressive episode; F32.9, depressive episode.
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