Journal of Affective Disorders 217 (2017) 55–59

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Mitochondrial genetic haplogroups and depressive symptoms: A large study among people in North America

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ARTICLE INFO

Keywords:
Mitochondrial haplogroups
Depression
Osteoarthritis initiative

ABSTRACT

Background: A possible relationship between mitochondrial haplogroups and psychiatric diseases (e.g. schizophrenia and bipolar disorder) has been postulated, but data regarding depression is still limited. We investigated whether any mitochondrial haplogroup carried a significant higher risk of depressive symptoms in a large prospective cohort of North American people included in the Osteoarthritis Initiative.

Methods: Cross sectional data was derived from the Osteoarthritis Initiative. The haplogroup was assigned through a combination of sequencing and PCR-RFLP techniques. All the mitochondrial haplogroups were named following this nomenclature: H, U, K, J, T, V, SuperHV, I, W, X or Others. Depression was ascertained through the 20-item Center for Epidemiologic Studies-Depression (CES-D), with ≥16 indicating depressive symptoms.

Results: Overall, 3601 Caucasian participants (55.9% women), mean age of 61.7 ± 9.3 years were included. No difference was observed in mitochondrial haplogroups frequency among those with depressive symptoms (n = 285, =7.9% of the baseline population) compared to participants with no depressive symptoms (N = 3316) (chi-square test = 0.53). Using a logistic regression analysis, adjusted for eight potential confounders, with those having the haplogroup H as the reference group (the most common haplogroup), no significant mitochondrial haplogroup was associated with prevalent depressive symptoms. The same results were evident in secondary analysis in which we matched depressed and non-depressed participants for age and sex.

Limitations: Cross-sectional design; only CES-D for evaluating mood; participants not totally representative of general population.

Conclusions: We found no evidence of any relationship between specific mitochondrial haplogroups and depressive symptoms. Future longitudinal research is required to confirm/ refute these findings.

1. Introduction

The human mitochondrial genome is a circular set of 16,569 base pairs encoding 37 genes and finally 13 proteins, involved in processes relevant to cellular function and survival. (Wang and Brinton, 2016) Similarly to nuclear DNA mitochondrial DNA (mtDNA) undergoes frequent mutations.(Copeland and Longley, 2014; Wang and Brinton, 2016) Mismatch, usually due to a recombination or repair, can lead to single nucleotide polymorphisms (SNPs) and clusters of these specific SNPs in the mitochondrial genome define the mitochondrial haplogroups. The evolution of mtDNA occurs at a much faster pace compared to the average nuclear DNA, and thus mutations have

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http://dx.doi.org/10.1016/j.jad.2017.03.069
Received 28 January 2017; Received in revised form 24 March 2017; Accepted 30 March 2017
Available online 04 April 2017
0165-0327/

accumulated sequentially, even if only along radiating maternal lineages. (Wallace and Chalkia, 2013) Therefore, it is hardly surprising that the biology of mitochondrial DNA may partly explain the genetic predisposition to certain medical conditions, probably in a similar way to the germline mutations of nuclear DNA (Luchini et al., 2016; Mafficini et al., 2016). Recent studies have proposed that the different mitochondrial haplogroups might play a role in the development of several chronic disease states (Mishmar et al., 2003; Picard et al., 2016; Wallace and Chalkia, 2013). Each of the mitochondrial haplogroups, in fact, is probably involved not only in mitochondria physiology, but also in cell metabolism (Horan and Cooper, 2014; Wallace, 2015). Thus, organs at high consumption of energy (such as brain) are the main target of mitochondrial dysfunction (Mink et al., 1981).

From an epidemiological viewpoint, several psychiatric conditions, such as schizophrenia and mood disorders have a preferential transmission through the maternal line (Kirk et al., 1999). Moreover, more recent studies reported that mood disorders are more frequent in maternal relatives of children with mitochondrial diseases, compared with their paternal relatives, or compared with maternal relatives of the children with other metabolic diseases (Grigoroiu-Serbanescu et al., 1998; Kato, 2001; Linnane et al., 1989). In this argument, some authors reported an increased mtDNA- copy number in peripheral cells and plasma in depressed (Cai et al., 2015; Nicod et al., 2016) and suicidal (Lindqvist et al., 2016) subjects. Finally, several mitochondrial encephalomyopathies are characterized by a high prevalence of bipolar disorder and depression (Kato, 2001). Taken together, these findings suggest that mitochondrial dysfunction may be associated with mood disorders, including depression.

Even if several experimental and pre-clinical pieces of research report that mitochondrial dysfunction is plausible in the development of depression (e.g. depressed people use less ATP in some brain regions) (Gardner et al., 2003; Karabatsiakis et al., 2014), only two studies have investigated an association between mitochondrial haplotypes and the presence of depression in human being not affected by mitochondrial myopathies (Rollins et al., 2009; Zhang et al., 2016). Although these studies reported a significant association between mitochondrial haplotypes and mental illness, they were limited in sample size suggesting that further research is needed.

Given this background, we aimed to investigate whether any mitochondrial haplogroup carried a significant higher risk of depressive symptoms in a large cohort of North American people included in the Osteoarthritis Initiative.

2. Methods

2.1. Data source and subjects

All participants in this cross-sectional study were recruited as part of the ongoing, publicly and privately funded, multicenter Osteoarthritis Initiative (OAI study) (http://www.oai.ucsf.edu/). The specific dataset used was the OAI baseline data (November 2008) (V00). The OAI recruited participants with/at high risk of knee osteoarthritis (e.g. obese, with familiarity for OA) from four clinical sites in the US (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. For this study, specific exclusion criteria are: pregnancy, presence of active rheumatoid arthritis, bilateral total knee replacement, unable to undergo knee magnetic resonance or to give a blood sample, any co-morbidity precluding the participation to the study and unwilling to sign the informed consent.

All participants provided written informed consent. The OAI study protocol was approved by the institutional review board of the OAI Coordinating Center, University of California at San Francisco.

2.2. Exposure

The haplogroup assignment was performed by a previously published method (Rego-Perez et al., 2008), which consisted in a combination of sequencing and PCR-RFLP techniques. The sequencing technique consisted in the multiplex assignment of the main 6 SNPs that contribute to the generation of the most prevalent Caucasian haplogroups (Torroni et al., 1996) (H, V, super HV, U, K, T, J) following the single base extension (SBE) assay. All the mitochondrial haplogroups have been named following this nomenclature in agreement with those suggested by the OAI (http://www.oai.ucsf.edu/): H, U, K, J, T, V, SuperHV, I, W, X or Others.

2.3. Outcome - depressive symptoms

The presence of depressive symptoms was derived from the 20-item Center for Epidemiologic Studies-Depression (CES-D) instrument. (Radloff, 1977) The range of possible values for this scores is 0–60, where higher scores indicate more depressive symptoms (Radloff, 1977). A cut-off of 16 is commonly used for the diagnosis of depressive symptoms (Radloff, 1977).

2.4. Covariates

A number of variables were identified from the OAI dataset to explore the relationship between mitochondrial haplogroups and depression. These included: (1) physical activity evaluated through the Physical Activity Scale for the Elderly (PASE) (Washburn et al., 1999). The PASE is validated in older populations, covers 12 different activities, such as walking, sports, and housework, and is scored from 0 to 400 and more; (2) race was defined as “white” vs. “others”; (3) smoking habits as “previous/current” vs. never; (4) educational level was categorized as “degree” vs. others; (5) yearly income as $< $ vs. $\geq$ 50,000 $ or missing data; (6) co-morbidities assessed through the modified Charlson comorbidity score, with higher scores indicating an increased severity of conditions (Katz et al., 1996); (7) body mass index (BMI), as recorded by a trained nurse.

2.5. Statistical analyses

For continuous variables, normal distributions were tested using the Kolmogorov-Smirnov test. The data are shown as means and standard deviations (SD) for quantitative measures, and percentages for all discrete variables by presence of depression. For continuous variables, Student's *T* test was used, whilst chi-square test was applied for discrete variables. Levene's test was used to test the homoscedasticity of variances and, if its assumption was violated, then Welch's ANOVA was used.

The strength of the association of mitochondrial haplogroups and depressive symptoms was assessed through a logistic regression analysis. Factors significantly associated with depression (taking a p-value < 0.05 as statistically significant) were included. Multi-collinearity among covariates was assessed through variance inflation factor, taking a cut-off of 2 as a reason of exclusion, but no variable was excluded due to this reason. The basic model was not adjusted for any confounders, while the fully adjusted model included baseline values of: age, BMI, PASE score, Charlson comorbidity index as continuous variables, and gender, education, smoking habits, yearly income as categorical variables. Data of logistic regression analysis were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

In a secondary analysis, we used controls (matched for age and sex) to depressed participants in order to attenuate the presence of any selection bias (Pearce, 2016).

All analyses were performed using the SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p-value < 0.05.