Author's Accepted Manuscript

MITOCHONDRIAL GENETIC HAPLOGROUPS AND DEPRESSIVE SYMPTOMS: A LARGE STUDY AMONG PEOPLE IN NORTH AMERICA

Nicola Veronese, Brendon Stubbs, Marco Solmi, Alberto Vaona, Jacopo Demurtas, Andre F. Carvalho, Ai Koyanagi, Trevor Thompson, Mario Zoratti, Stefania Maggi

Cite this article as: Nicola Veronese, Brendon Stubbs, Marco Solmi, Alberto Vaona, Jacopo Demurtas, Andre F. Carvalho, Ai Koyanagi, Trevor Thompson, Mario Zoratti and Stefania Maggi, MITOCHONDRIAL GENETIC HAPLOGROUPS AND DEPRESSIVE SYMPTOMS: A LARGE STUDY AMONG PEOPLE IN NORTH AMERICA, *Journal of Affective Disorders* http://dx.doi.org/10.1016/j.jad.2017.03.069

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

MITOCHONDRIAL GENETIC HAPLOGROUPS AND DEPRESSIVE SYMPTOMS: A

LARGE STUDY AMONG PEOPLE IN NORTH AMERICA

Nicola Veronese[a,b*], Brendon Stubbs[c,d,e], Marco Solmi[b,f,g], Alberto Vaona[h], Jacopo Demurtas[i], Andre F Carvalho[j], Ai Koyanagi[k], Trevor Thompson[l], Mario Zoratti[a,m], Stefania Maggi[a]

[a]National Research Council, Neuroscience Institute, Aging Branch, Padova, Italy.

[b]Institute for clinical Research and Education in Medicine (IREM), Padova, Italy.

[c]South London and Maudsley NHS FoundationTrust, Denmark Hill, London SE5 8AZ, United Kingdom.

[d]Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London SE5 8 AF, United Kingdom.

[e]Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, United Kingdom.

[f]Department of Neurosciences, University of Padova, Padova, Italy.

[g]National Health Care System, Padua Local Unit ULSS 17, Italy.

[h]Primary Care Department, Azienda ULSS20 Verona, Verona, Italy.

[i]Primary Care Department, Azienda USL Toscana Sud Est, Grosseto, Italy.

[j]Translational Psychiatry Research Group, Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceara, Fortaleza, CE, Brazil.

1

[k]Research and Development Unit, Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, CIBERSAM, Barcelona, Spain.

[l]Faculty of Education and Health, University of Greenwich, London, United Kingdom.

[m]Department of Biomedical Sciences, University of Padova, Padova, Italy.

[*]Corresponding author: National Research Council, Neuroscience Institute, Aging Branch, Padova, Italy. Via Giustiniani, 2 - 35128 Padova, Italy. Tel.: +39 0498211776; fax: +39 0498211218. ilmannato@gmail.com

2

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 $\geq$16 indicating depressive symptoms.

Results

Overall, 3,601 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=3,316) (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.

Keywords: mitochondrial haplogroups; depression; osteoarthritis initiative.

4

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 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.

METHODS

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.

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.

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 to 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)

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.

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.

RESULTS

Study participants

At baseline, among 4,796 potentially eligible individuals, 1,047 subjects did not have a mitochondrial DNA assessment, 126 did not have this assessment for technical problems and 22 did not have information regarding CES-D. Thus, 3,601 participants were enrolled in the current study. Compared to those included in this analysis, the 1,195 people not enrolled were not significantly differences in terms of age and gender, but there was a higher presence of non-Caucasian ethnicities (chi-square test, p<0.0001) (details not shown).

Baseline analyses

The 3,601 participants included aged a mean of 61.7±9.3 (range: 45-79) years, with a slight higher prevalence of women (=55.9%). All participants were Caucasians.

Participants were divided into those with depressive symptoms (n=285, 7.9% of the sample) and without (n=3,316). The baseline characteristics of both groups are summarized in **Table 1.** Briefly, people with depressive symptoms were significantly older, more likely to be females, and obese compared to the non-depressed group. People with depressive symptoms were more frequently smokers, with a lower educational level, poorer and with more comorbidities than those with no depressive symptoms (**Table 1**).

Association between mitochondrial haplogroups and depression

11

As reported in **Figure 1**, no significant differences emerged regarding in the prevalence of mitochondrial haplogroups (chi-square test=0.53). For example, the most frequent haplogroup (i.e. H) had the same prevalence among the depressed and no depressed (42.5% in both groups).

Using a logistic regression analysis, adjusted for eight potential confounders, with those having the haplogroup H as the reference, no significant mitochondrial haplogroup was associated with a prevalent depressive symptoms. The OR ranged from 0.50 (95%CI: 0.18-1.43) of other haplogroup to 1.74 (95%CI: 0.75-4.07) of haplogroup W (**Table 2**).

In a secondary analysis, we explored whether using controls matched for age and sex, influenced our results, but the association between mitochondrial haplogroups and depressive symptoms remained not significant (**Table 2**).

DISCUSSION

In this large cross-sectional paper, we found there was no significant association between mitochondrial haplotypes and depressive symptoms. Our findings remained unaltered after adjusting for potential confounders or using controls matched for sex and age. Thus, our data suggest that mitochondria haplogroups may not be related to depressive symptoms.

The interest of mitochondrial haplotypes in the development of psychiatric diseases is rapidly increasing. Several studies have reported that mitochondrial haplotypes are associated with the presence of some psychiatric conditions, particularly schizophrenia and bipolar disorder.(Clay et al., 2011; Rajasekaran et al., 2015) The mechanisms linking mitochondrial haplogroups and related dysfunction and these conditions may be attributed to altered oxidative/nitrosative stress responses which could activate the immunoinflammatory pathways (Bano et al., 2017; Soysal et al.; Soysal et al., 2016) and subsequently lead to neuroprogressive changes, typical of bipolar disorder and schizophrenia. (Clay et al., 2011; Rajasekaran et al., 2015) Since the same mechanisms are relevant for the development of depression, some researchers have tried to disentangle if any association exists between mitochondrial haplogroups and depressive mood. These studies, however, are very limited and included few participants. Initially Suomalainen et al. reported in a family affected by a chronic progressive ophthalmoplegia that the presence of depression was very common. (Suomalainen et al., 1992) These authors interpreted this finding as a possible sign of mitochondrial encephalopathy. Similarly, Suzuki and collaborators investigated 15 people affected by a form of mitochondrial diabetes founding that four of them were affected by mood disorders. (Suzuki et al., 1997) More recently, Rollins et al. showed that, in a peculiar subgroup of patients with schizophrenia, the rate of synonymous base pair substitutions in the coding regions of the mtDNA genome was significantly higher compared to controls. (Rollins et al., 2009). However the same

13

results were not confirmed in patients with depression compared with controls. These findings highlight the concept of a higher mtDNA instability in some mental disorders. Finally, in 2016, Zhang et al., reported in 744 Chinese subjects with major depression matched with 767 Chinese healthy controls that the T-C haplotype was significantly associated with depression.(Zhang et al., 2016) Contrary to results reported by Zhang et al, we did not find any significant association between mitochondrial haplogroups and depressive symptoms in our study. Several hypotheses could explain our findings. First, the studies cited before (except the last two) were made among populations affected by mitochondrial diseases and without a control group. Therefore, it is difficult to say whether a particular mitochondrial haplogroup is associated or not with depression. Second, since our knowledge regarding the possible effect of mitochondrial haplotypes on depression derives from the reported similarities with other psychiatric diseases and from some indirect findings (such as people with depression have reduced blood flow and metabolism in the prefrontal cortex compared to healthy controls)(Videbech, 2000), thus it is possible that mitochondrial haplotypes do not play a role in the development of this disease. It is noteworthy, for example, that Stine et al. in postmortem samples found no significant alterations in mtDNA in nine depressed people who completed suicide compared to controls.(Stine et al., 1993) However our study suggests further studies are required to disentangle the potential relationship between mitochondria haplogroups and depression. Moreover, Zhang et al compared patients with a full diagnosis of MDD with healthy controls, thus including people with more pronounced depressive illness than ours which included people with depressive symptoms.(Zhang et al., 2016) Also, while we focused on a Caucasian population, Zhang et al focused on a Chinese sample, which might have different mithocondrial haplotypes' distribution. (Zhang et al., 2016) Furthermore, we did not account for stress in our analyses; since it has been suggested that stress can modify amount of mtDNA, our findings may have been biased by neglecting stress as confounding factor. Finally, it may be that

there were too few participants within each mitochondria haplogroups and thus some of our analyses were underpowered.

A special consideration should also account for the close relation between mithocondrial functioning and ageing, in elderly population. Ageing is per sè associated with a weakened mitochondrial efficiency(Chistiakov et al., 2014), and mitochondrial age-related impairment may also play a role in depression onset(Harper et al., 2016), beyond haplotypes' distribution.

Limitations

The findings of our paper should be interpreted within its limitations. First, the diagnosis of depressive symptoms was made only using the CES-D that, however, includes many symptoms defined by the (DSM-V) for a major depressive episode and therefore is somewhat justifiable(Veronese et al., 2016). Second, we did not assess the role of medications used for depression and this could introduce an important bias. Third, the number of people in some haplogroups was limited. Fourth, the medical diseases in the OAI are self-reported, and this could introduce another potential bias. Fifth, data was only available of mitochondrial haplogroups among Caucasians and the results do not extend beyond this ethnicity. Sixth, the OAI did not contain detailed information regarding other psychiatric diseases that seem to be associated with mitochondrial haplogroups and this could affect our results. Finally, the OAI included only people with or at high risk of knee osteoarthritis and so it could be not fully representative of the general population.

In conclusion, in this large cohort study we did not find a relationship between any mitochondrial haplogroups with depressive symptoms. Further research with different diagnostic criteria for depression and with a longitudinal design are needed to disentangle if any mitochondrial haplotype is associated with depression.

Bano, G., Trevisan, C., Carraro, S., Solmi, M., Luchini, C., Stubbs, B., Manzato, E., Sergi, G., Veronese, N., 2017. Inflammation and sarcopenia: A systematic review and meta-analysis. Maturitas 96, 10-15.

Cai, N., Chang, S., Li, Y., Li, Q., Hu, J., Liang, J., Song, L., Kretzschmar, W., Gan, X., Nicod, J., Rivera, M., Deng, H., Du, B., Li, K., Sang, W., Gao, J., Gao, S., Ha, B., Ho, H.Y., Hu, C., Hu, J., Hu, Z., Huang, G., Jiang, G., Jiang, T., Jin, W., Li, G., Li, K., Li, Y., Li, Y., Li, Y., Lin, Y.T., Liu, L., Liu, T., Liu, Y., Liu, Y., Lu, Y., Lv, L., Meng, H., Qian, P., Sang, H., Shen, J., Shi, J., Sun, J., Tao, M., Wang, G., Wang, G., Wang, J., Wang, L., Wang, X., Wang, X., Yang, H., Yang, L., Yin, Y., Zhang, J., Zhang, K., Sun, N., Zhang, W., Zhang, X., Zhang, Z., Zhong, H., Breen, G., Wang, J., Marchini, J., Chen, Y., Xu, Q., Xu, X., Mott, R., Huang, G.J., Kendler, K., Flint, J., 2015. Molecular signatures of major depression. Current biology : CB 25, 1146-1156.

Chistiakov, D.A., Sobenin, I.A., Revin, V.V., Orekhov, A.N., Bobryshev, Y.V., 2014. Mitochondrial aging and age-related dysfunction of mitochondria. Biomed Res Int 2014, 238463.

Clay, H.B., Sillivan, S., Konradi, C., 2011. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience 29, 311-324.

Copeland, W.C., Longley, M.J., 2014. Mitochondrial genome maintenance in health and disease. DNA repair 19, 190-198.

Gardner, A., Johansson, A., Wibom, R., Nennesmo, I., von Döbeln, U., Hagenfeldt, L., Hällström, T., 2003. Alterations of mitochondrial function and correlations with personality traits in selected major depressive disorder patients. Journal of Affective Disorders 76, 55-68.

Grigoroiu-Serbanescu, M., Martinez, M., Nothen, M.M., Propping, P., Milea, S., Mihailescu, R., Marinescu, E., 1998. Patterns of parental transmission and familial aggregation models in bipolar affective disorder. American journal of medical genetics 81, 397-404.

Harper, D.G., Joe, E.B., Jensen, J.E., Ravichandran, C., Forester, B.P., 2016. Brain levels of high-energy phosphate metabolites and executive function in geriatric depression. Int J Geriatr Psychiatry 31, 1241-1249.

Horan, M.P., Cooper, D.N., 2014. The emergence of the mitochondrial genome as a partial regulator of nuclear function is providing new insights into the genetic mechanisms underlying age-related complex disease. Human genetics 133, 435-458.

Karabatsiakis, A., Bock, C., Salinas-Manrique, J., Kolassa, S., Calzia, E., Dietrich, D.E., Kolassa, I.T., 2014. Mitochondrial respiration in peripheral blood mononuclear cells correlates with depressive subsymptoms and severity of major depression. Translational psychiatry 4, e397.

Kato, T., 2001. The other, forgotten genome: mitochondrial DNA and mental disorders. Molecular psychiatry 6, 625-633.

Katz, J.N., Chang, L.C., Sangha, O., Fossel, A.H., Bates, D.W., 1996. Can comorbidity be measured by questionnaire rather than medical record review? Medical care 34, 73-84.

Kirk, R., Furlong, R.A., Amos, W., Cooper, G., Rubinsztein, J.S., Walsh, C., Paykel, E.S., Rubinsztein, D.C., 1999. Mitochondrial genetic analyses suggest selection against maternal lineages in bipolar affective disorder. American journal of human genetics 65, 508-518.

Lindqvist, D., Fernström, J., Grudet, C., Ljunggren, L., Träskman-Bendz, L., Ohlsson, L., Westrin, Å., 2016. Increased plasma levels of circulating cell-free mitochondrial DNA in suicide attempters: associations with HPA-axis hyperactivity. Translational psychiatry 6, e971.

Linnane, A.W., Marzuki, S., Ozawa, T., Tanaka, M., 1989. Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. Lancet (London, England) 1, 642-645.

Luchini, C., Veronese, N., Yachida, S., Cheng, L., Nottegar, A., Stubbs, B., Solmi, M., Capelli, P., Pea, A., Barbareschi, M., Fassan, M., Wood, L.D., Scarpa, A., 2016. Different Prognostic Roles Of Tumor Suppressor Gene BAP1 In Cancer: A Systematic Review With Meta-Analysis. Genes, chromosomes & cancer.

Mafficini, A., Simbolo, M., Parisi, A., Rusev, B., Luchini, C., Cataldo, I., Piazzola, E., Sperandio, N., Turri, G., Franchi, M., Tortora, G., Bovo, C., Lawlor, R.T., Scarpa, A., 2016. BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next-generation sequencing. Oncotarget 7, 1076-1083.

Mink, J.W., Blumenschine, R.J., Adams, D.B., 1981. Ratio of central nervous system to body metabolism in vertebrates: its constancy and functional basis. The American journal of physiology 241, R203-212.

Mishmar, D., Ruiz-Pesini, E., Golik, P., Macaulay, V., Clark, A.G., Hosseini, S., Brandon, M., Easley, K., Chen, E., Brown, M.D., Sukernik, R.I., Olckers, A., Wallace, D.C., 2003. Natural selection shaped regional mtDNA variation in humans. Proceedings of the National Academy of Sciences of the United States of America 100, 171-176.

Nicod, J., Wagner, S., Vonberg, F., Bhomra, A., Schlicht, K.F., Tadic, A., Mott, R., Lieb, K., Flint, J., 2016. The Amount of Mitochondrial DNA in Blood Reflects the Course of a Depressive Episode. Biological psychiatry 80, e41-42.

Pearce, N., 2016. Analysis of matched case-control studies. Bmj 352, i969.

Picard, M., Wallace, D.C., Burelle, Y., 2016. The rise of mitochondria in medicine. Mitochondrion 30, 105-116.

Radloff, L.S., 1977. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement 1, 385-401.

Rajasekaran, A., Venkatasubramanian, G., Berk, M., Debnath, M., 2015. Mitochondrial dysfunction in schizophrenia: pathways, mechanisms and implications. Neuroscience and biobehavioral reviews 48, 10-21.

Rego-Perez, I., Fernandez-Moreno, M., Fernandez-Lopez, C., Arenas, J., Blanco, F.J., 2008. Mitochondrial DNA haplogroups: role in the prevalence and severity of knee osteoarthritis. Arthritis and rheumatism 58, 2387-2396.

Rollins, B., Martin, M.V., Sequeira, P.A., Moon, E.A., Morgan, L.Z., Watson, S.J., Schatzberg, A., Akil, H., Myers, R.M., Jones, E.G., Wallace, D.C., Bunney, W.E., Vawter, M.P., 2009. Mitochondrial variants in schizophrenia, bipolar disorder, and major depressive disorder. PloS one 4, e4913.

Soysal, P., Isik, A.T., Carvalho, A.F., Fernandes, B.S., Solmi, M., Schofield, P., Veronese, N., Stubbs, B., Oxidative Stress And Frailty: A Systematic Review And Best Evidence Synthesis. Maturitas.

Soysal, P., Stubbs, B., Lucato, P., Luchini, C., Solmi, M., Peluso, R., Sergi, G., Isik, A.T., Manzato, E., Maggi, S., Maggio, M., Prina, A.M., Cosco, T.D., Wu, Y.-T., Veronese, N., 2016. Inflammation And Frailty In The Elderly: A Systematic Review And Meta-analysis. Ageing research reviews.

Stine, O.C., Luu, S.U., Zito, M., Casanova, M., 1993. The possible association between affective disorder and partially deleted mitochondrial DNA. Biological psychiatry 33, 141-142.

Suomalainen, A., Majander, A., Haltia, M., Somer, H., Lonnqvist, J., Savontaus, M.L., Peltonen, L., 1992. Multiple deletions of mitochondrial DNA in several tissues of a patient with severe retarded depression and familial progressive external ophthalmoplegia. The Journal of clinical investigation 90, 61-66.

Suzuki, Y., Taniyama, M., Muramatsu, T., Atsumi, Y., Hosokawa, K., Asahina, T., Shimada, A., Murata, C., Matsuoka, K., 1997. Diabetes mellitus associated with 3243 mitochondrial tRNA(Leu(UUR)) mutation: clinical features and coenzyme Q10 treatment. Molecular aspects of medicine 18 Suppl, S181-188.

Torroni, A., Huoponen, K., Francalacci, P., Petrozzi, M., Morelli, L., Scozzari, R., Obinu, D., Savontaus, M.L., Wallace, D.C., 1996. Classification of European mtDNAs from an analysis of three European populations. Genetics 144, 1835-1850.

Veronese, N., Stubbs, B., Solmi, M., Smith, T.O., Noale, M., Cooper, C., Maggi, S., 2016. Association between lower limb osteoarthritis and incidence of depressive symptoms: data from the osteoarthritis initiative. Age and ageing.

Videbech, P., 2000. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. Acta psychiatrica Scandinavica 101, 11-20.

Wallace, D.C., 2015. Mitochondrial DNA variation in human radiation and disease. Cell 163, 33-38.

Wallace, D.C., Chalkia, D., 2013. Mitochondrial DNA genetics and the heteroplasmy conundrum in evolution and disease. Cold Spring Harbor perspectives in biology 5, a021220.

Wang, Y., Brinton, R.D., 2016. Triad of Risk for Late Onset Alzheimer's: Mitochondrial Haplotype, APOE Genotype and Chromosomal Sex. Frontiers in aging neuroscience 8, 232.

Washburn, R.A., McAuley, E., Katula, J., Mihalko, S.L., Boileau, R.A., 1999. The physical activity scale for the elderly (PASE): evidence for validity. Journal of clinical epidemiology 52, 643-651.

21

Zhang, Z., Ni, J., Zhang, J., Tang, W., Li, X., Wu, Z., Zhang, C., 2016. A haplotype in the 5'-upstream region of the NDUFV2 gene is associated with major depressive disorder in Han Chinese. J Affect Disord 190, 329-332.

Figure 1. Prevalence of depressive symptoms by mitochondrial haplogroups.

The prevalence of each haplogroup is represented as percentage in people with depressive symptoms or not.

Table 1. Baseline characteristics by depression status.

Variable	Depressive symptoms (n=285)	No depressive symptoms (n=3316)	p-value
Age (years)	61.9 (9.3)	59.3 (9.3)	<0.0001
Females (%)	63.2	55.3	0.001
BMI (Kg/m^2)	29.1 (5.5)	28.0 (4.5)	<0.0001
White race (%)		All whites	
PASE (points)	156.5 (81.1)	164.1 (80.0)	0.13
Smoking (%)	55.6	45.5	0.001
Degree (%)	24.6	34.3	0.001
Yearly income (<50,000 $)	46.5	68.7	<0.0001
Charlson co-morbidity score	0.5 (0.8)	0.3 (0.8)	<0.0001

23

Notes:

Numbers are mean values (and standard deviations) or percentages, as appropriate.

Abbreviations: BMI: body mass index; PASE: physical activity scale for the elderly; CES-D: Center for Epidemiological Studies Depression.

Table 2. Association between mitochondrial haplogroups and Depressive symptoms .

	All cohort	*Matched (for age and sex)*

	Unadjusted OR (95%CI)	P value	Fully-adjusted OR[*] (95%CI)	P value	Unadjusted OR (95%CI)	P value	Fully-adjusted OR[*] (95%CI)	P value
H	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
I	0.77 (0.23-2.50)	0.66	0.57 (0.17-1.91)	0.36	0.51 (0.15-1.74)	0.29	0.37 (0.11-1.28)	0.12
J	1.05 (0.67-1.64)	0.83	0.99 (0.63-1.56)	0.97	1.00 (0.62-1.62)	0.99	0.93 (0.56-1.52)	0.76
K	1.21 (0.77-1.91)	0.41	1.32 (0.83-2.11)	0.24	1.30 (0.79-2.13)	0.31	1.36 (0.81-2.28)	0.25
Others	0.61 (0.22-1.70)	0.35	0.50 (0.18-1.43)	0.20	0.72 (0.24-2.12)	0.55	0.45 (0.14-1.43)	0.18
SuperHV	1.39 (0.72-2.67)	0.33	1.22 (0.63-2.38)	0.56	1.08 (0.54-2.18)	0.82	1.07 (0.52-2.22)	0.85
T	0.99 (0.65-1.51)	0.97	1.02 (0.66-1.57)	0.94	0.95 (0.61-1.50)	0.83	0.94 (0.58-1.50)	0.78

	All cohort				Matched (for age and sex)			
	Unadjusted OR (95%CI)	P value	Fully-adjusted OR[*] (95%CI)	P value	Unadjusted OR (95%CI)	P value	Fully-adjusted OR[*] (95%CI)	P value
U	0.76 (0.52-1.11)	0.16	0.78 (0.53-1.14)	0.20	0.84 (0.56-1.27)	0.41	0.82 (0.54-1.50)	0.37
V	0.89 (0.42-1.88)	0.89	0.83 (0.39-1.79)	0.64	0.66 (0.30-1.43)	0.29	0.56 (0.25-1.27)	0.17
W	1.91 (0.84-4.35)	0.12	1.74 (0.75-4.07)	0.20	2.12 (0.83-5.44)	0.12	2.17 (0.80-5.91)	0.13
X	1.15 (0.40-3.26)	0.80	1.07 (0.36-3.15)	0.91	1.05 (0.34-3.23)	0.93	1.00 (0.32-3.21)	0.99

Notes:

All the data are presented as odds ratios (ORs) with their 95% confidence intervals.

[*]Fully-adjusted model included as covariates: age (as continuous); sex; body mass index (as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly
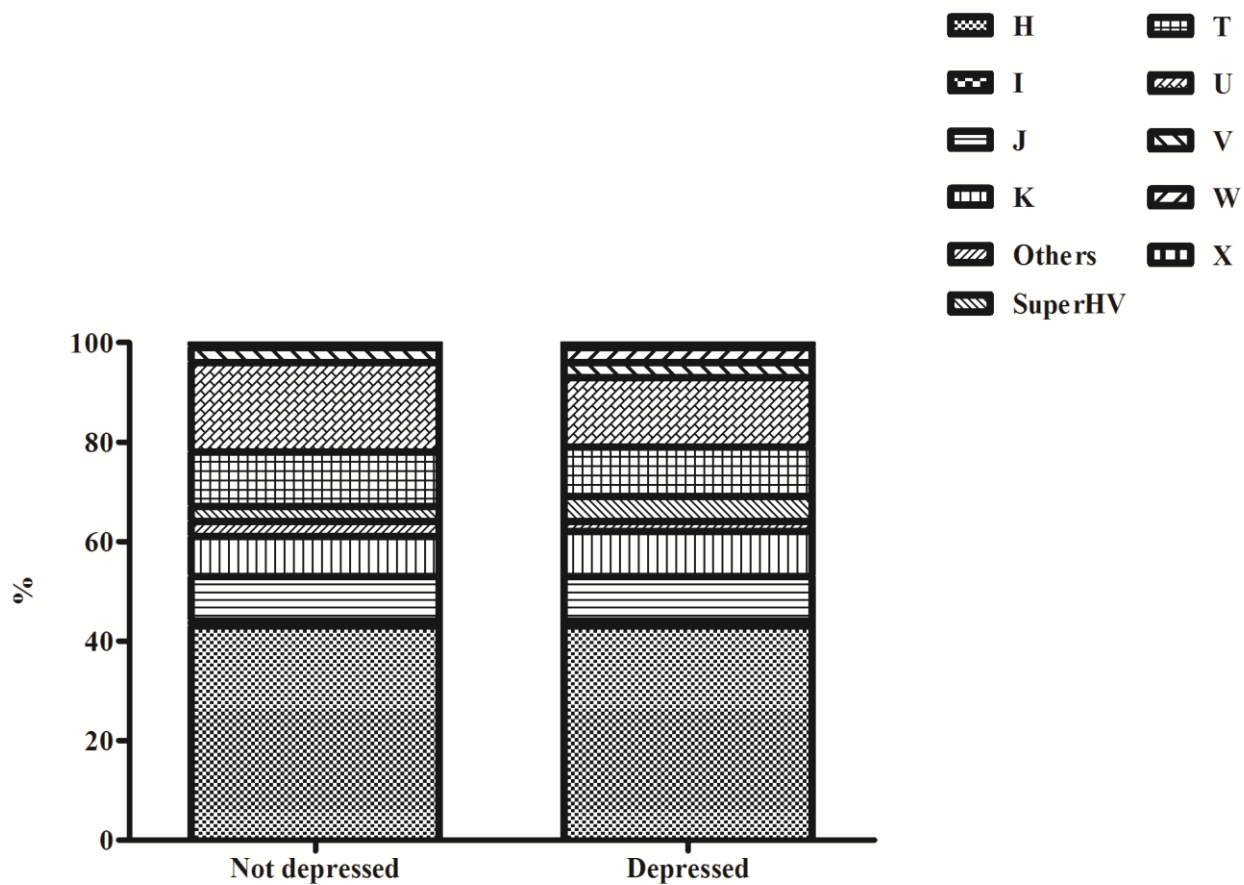
26

income (categorized as $\geq$ or $<$ 50,000\$ and missing data); Physical Activity Scale for Elderly score

(as continuous); Charlson co-morbidity index.

Abbreviations: CI: confidence intervals; OR: odds ratio.

Highlights

- Limited data is available regarding mitochondrial haplogroups and depression.

- In our study, no association was found between mitochondrial haplogroups and depression.

- Future longitudinal studies are needed.