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Common mitochondrial haplogroups as modifiers of the onset-age for critical COVID-19

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ABSTRACT

As a key regulator of innate immunity, mitochondrial function is essential to maintain antiviral activities. Common mitochondrial DNA variants (haplogroups) have been associated with different physiological capacities and the risk of developing several diseases. Haplogroup H was associated with increased survival among sepsis patients, and lower risk of progression toward AIDS in HIV infected and lower manifestation of severe manifestation of herpes virus disease. We studied 316 Spanish with critical COVID-19, and found that the 7028C (haplogroup H) was protective among patients with early-onset disease (≤ 65 vs > 65 years, $p = 0.01$), while the ancestral 16223T was a risk factor for early-onset critical COVID-19 (OR = 3.36, 95 %CI = 1.49–7.54). Our work suggested that common mitochondrial variants may serve as predictors of COVID-19 severity. Additional studies to confirm this effect from other populations are of special interest.

1. Introduction

In addition to their primary function as energy producers and regulators of cellular processes such as apoptosis and ageing, mitochondria play an important role in the vertebrates innate immunity (Koshiba, 2013). The presence of virus inside the cell is detected by a group of cytosolic proteins that bind to and activate the **mitochondrial antiviral-signaling protein (MAVS)** located in the inner membrane of the mitochondria (Moore and Ting, 2008). Activated MAVS trigger the secretion of immunomodulators such as type I interferons and proinflammatory cytokine that would clear the viruses and limit the infection damage (Belgnaoui et al., 2011). The mitochondrion membrane potential is also essential to activate these immunological pathways (Schneider et al., 2019; Hu et al., 2019). Many viruses can interfere with mitochondrial function to impair the antiviral activity. For instance, the PB1-F2 influenza A protein targets the mitochondria and induces apoptosis and impaired cellular innate immunity (Yoshizumi et al., 2014; Zamarin et al., 2005).

Cytomegalovirus impairs MAVS through the viral apoptosis proteins that localizes in the mitochondria and reduces the pro-inflammatory response (Choi et al., 2018). Several SARS-CoV-1 proteins such as ORF3b and ORF-9b localizes into host mitochondria and suppresses innate immunity by manipulating the MAVS, while other mitochondrial localized viral proteins enhance infection by promoting viral replication (Shi et al., 2014; Chen et al., 2007).

Cells infected by SARS-CoV-2 exhibit a mitochondrial dysfunction with mitochondrial membrane depolarization, mitochondrial permeability transition pore opening and increased release of reactive oxygen species (ROS) (Shang et al., 2022). Interestingly, the SARS-CoV-2 membrane (M) protein would induce lung epithelial cells apoptosis by promoting the translocation of pro-apoptotic proteins into mitochondria (Yang et al., 2022). This would exacerbate the lung and other organs damage that characterizes the severe manifestation of COVID-19 (Mo et al., 2022; Costa et al., 2022).

The clinical features of COVID-19 caused by SARS-CoV-2 range from an asymptomatic state to severe pneumonia and multiorgan dysfunction

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with hospital admission (Zeng et al., 2021). The most severe cases would require respiratory support in the ICU and are at high risk of death. This heterogeneous symptoms might be partly explained by the individual’s hereditary susceptibility, and several nuclear-encoded genes have been associated with COVID-19 severity and death (COVID-19 Host Genetics Initiative, 2021; Wang et al., 2020). The mitochondria innate antioxidant and immune capacities could also play a role in the susceptibility, and in this regard the mitochondrial DNA variants might serve as susceptibility markers for severe COVID-19. Common mtDNA variants define the mtDNA haplogroups and have been related with different mitochondrial-mediated capacities, such as ROS and ATP production (Kenney et al., 2014; Kenney et al., 2014; Krzywanski et al., 2016). These mtDNA variants have been associated with the risk of developing common diseases and might also contribute to define the lifespan (Yonova-Doing et al., 2021).

The effect of mtDNA variants on viral-mediated disease has been previously addressed. Among others, manifestations of AIDS, herpes, and COVID-19 could be regulated by the mtDNA variation (Hendrickson et al., 2008; Medrano et al., 2018; Hart et al., 2013; Levinson et al., 2016; Wu et al., 2021; Dirican et al., 2022).

Here, we determined the association of the common European haplogroups with severe COVID-19 and death among SARS-CoV-2 infected.

2. Patients and methods

We obtained the demographic and clinical data of 316 patients who required admission in the intensive care unit (ICU) due to COVID-19 (mean age 64, range 24–95). These patients were hospitalised between March-2020 and April-2021, period in which three pandemic waves took place in our community. They were followed till disease remission with hospital discharge or death. Following previously reported criteria we considered early-onset COVID-19 as an age < 65 years (Gentilotti et al., 2021).

All the participants were of European ancestry and from the region of

Asturias (Northern Spain, total population 1 million). The study was approved by the Ethics Committee of Principado de Asturias (Oviedo, Spain). All the patients (or their next of kin) and controls gave their consent to participate in the study. The controls were recruited from the general population with the only purpose of defining the mtDNA variant frequencies, and no data about common traits or clinical manifestations were considered. Although we did not determine the existence of SARS-CoV-2 infection, none of the controls required hospitalization due to COVID-19. In order to avoid the possibility of age-bias we compared patients and controls within the same age-range.

2.1. Haplogroups classification

Five mtDNA single nucleotide polymorphisms (SNPs G4580A, C7028T, A12308G, G13368A, and G13708A) were used to determine the most common European mitochondrial haplogroups (see supplementary file methods and the mitomap database for haplogroups definition; www.mitomap.org). Individuals who were 7028C were considered as haplogroup H, and 7028T were further classified as J, KU, T, V, IWX, or other based on the variants combinations (supplementary table). These were also genotyped for the T16223C that differentiates the macro-haplogroup R (16223C) from the ancestral macro-haplogroup N (16223T) (Fig. 1).

2.2. Statistical analysis

The statistical analysis was performed with the R free software (www.r-project.org). The logistic regression (linear generalized model, LGM) was used to compare mean values and frequencies between the groups.

3. Results

The main characteristics of the patients are summarised in Table 1.

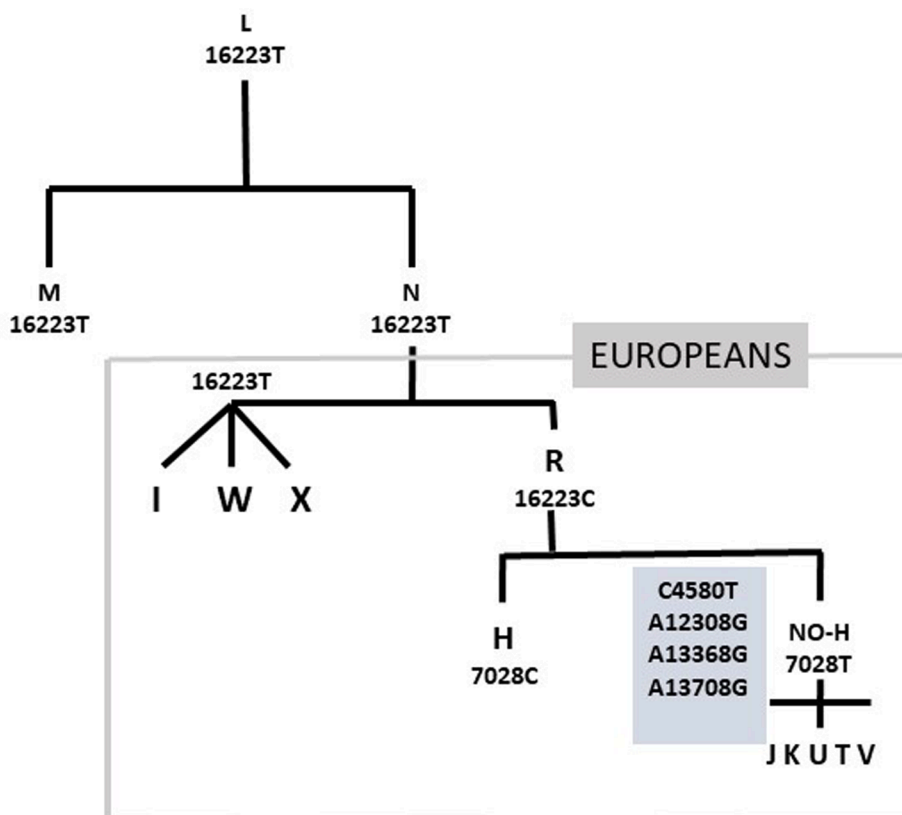


Fig. 1. Evolution of the common European haplogroups from the ancestral African L. N originated about 65,000 years ago and is the ancestral for the out-of-Africa haplogroups. The R lineage originated about 60,000 years ago in the Middle East and is characterised by several nucleotide changes, such as 16223C. Most of the common European haplogroups derived from R, including the H lineage (7028C) that surged about 20,000 years ago in Southwest Asia and is currently present in 40–50 % of Europeans.

Table 1

Main values in the 316 COVID-19 patients. PO_2/FiO_2 = ratio of arterial oxygen partial pressure (PaO₂, mmHg) to fractional inspired oxygen (FiO₂). Moderate/severe hypoxemia, <300.

	≤65 years N = 148	>65 years N = 168	p-value
Male	104 (70 %)	125 (74 %)	0.41
Female	(30 %) 44	(26 %) 43	
Age Median years	57	73	
(range)	(25–65)	(66–91)	
BMI median	29 (19–55)	31(19–53)	0.01
(range)			
BMI > 30	81 (41 %)	68 (55 %)	0.012
Diabetes	20 (13 %)	44 (26 %)	0.005
Hypercholesterolemia	51 (34 %)	91 (54 %)	0.0004
Hypertension	57 (39 %)	115 (69 %)	<0.0001
Death	13 (9 %)	54 (32 %)	<0.0001
PO₂/FiO₂ < 300	26 (17 %)	34 (20 %)	0.43

All the participants were first genotyped from the C7028T that defines the most common European haplogroup H (7028C) (Table 2). 7028T patients had a significantly lower mean age than 7028C (63 vs 67 years; $p = 0.002$). We found a non-significantly higher frequency of the 7028T among the early-onset patients (≤65 years) compared to matched controls ($p = 0.11$), and a significantly higher frequency compared to the elderly patients ($p = 0.01$). This difference was not attributable to an age-effect in the general population because we did not find differences between controls younger or older than 65 years (47 % and 45 %, respectively). The mtDNA 7028C (haplogroup H) was thus protective for developing severe COVID-19 at an age ≤ 65.

The 7028T were further genotyped for the mtDNA variants to determine the non-H haplogroups (J, KU, T, V, and WXI). We found a higher frequency of the IWX haplogroups in the patients compared to their age matched controls ($p < 0.002$, OR = 3.36, 95 %CI = 1.49–7.54). There was a significantly higher IWX frequency in the younger vs elderly patients (15 % vs 9 %, $p = 0.03$). Haplogroups frequencies were non significantly different between elderly patients and controls (Table 2). The IWX haplogroups are characterised by 16223T, that is the ancestral allele compared to the 16223C that characterises the macro-haplogroup R that rooted the main European haplogroups (Fig. 1). In our population, 16223T was a marker for early-onset severe COVID-19 with frequencies 15 % and 9 % in patients younger and older than 65 years, and mean ages of 57 years (16223T) and 66 years (16223C) ($p = 0.006$) (Fig. 2).

Table 2

Frequency of the mtDNA variants in the ICU patients and population controls. All them were genotyped for the 7028 variant (C = haplogroup H). The 7028T were genotyped for the G4580A, A12308G, G13368A, G13708A, and C16223T variants to determine the common non-H haplogroups (see suppl. file methods).

	≤65 years		>65 years	
	Covid-19 N = 148	Controls N = 182	Covid-19 N = 168	Controls N = 181
7028C	57 (39 %)	86 (47 %)	88 (52 %)	82 (45 %)
7028T	91 (61 %)	96 (53 %)	80 (48 %)	99 (55 %)
p-value (T)OR (95 %CI)	p = 0.11 OR = 1.43 (0.92–2.22)		p = 0.19 OR = 0.75 (0.49–1.15)	
16223T	22 (15 %)	9 (5 %)	12 (8 %)	9 (5 %)
16,223C	126 (85 %)	173 (95 %)	156 (92 %)	172 (95 %)
p-value (T) OR (95 %CI)	p = 0.002 OR = 3.36 (1.49–7.54)		p = 0.39 OR = 1.47 (0.60–3.59)	
J	18 (12 %)	28(15 %)	12 (7 %)	17 (9 %)
K + U	32 (22 %)	47(26 %)	30 (18 %)	46 (25 %)
T	6 (4 %)	7 (4 %)	17 (10 %)	19 (10 %)
V	3 (2 %)	2 (1 %)	4(2 %)	6 (3 %)
IWX	22 (15 %)	9(5 %)	12 (9 %)	9 (6 %)
OTHER	10 (6 %)	3(2 %)	5 (2 %)	2 (2 %)

patients ≤ 65 vs. > 65 years: C7028T, $p = 0.01$; C16223T, $p = 0.03$.

We determined the association between the main cardiovascular traits and antropometric values and the mtDNA haplogroups. The multiple logistic regression including age as a covariate showed that none of the variables was associated with the mtDA variants in the whole cohort (supplementary table). The mtDNA variants were not associated with an increased risk of death, although the number of deceased patients in the younger group ($n = 13$) was too low to conclude statistical associations.

4. Discussion

The main finding of our study was the significant protective effect of the 7028C variant (haplogroup H) for early onset critical COVID-19. The risk effect of non-H haplogroups was further attributed to an increased frequency of 16223T (haplogroups IWX) among the younger patients. The age-dependent association of nuclear gene variants with severe COVID-19 has been reported, including the main genetic risk factor in chromosome 3 (Nakanishi et al., 2021).

The 16223T differentiates the ancestral R and non-R haplogroups, represented by the WXI that is rare among the Europeans. Interestingly these mtDNA variants were associated with risk of herpes virus disease (Levinson et al., 2016). In a large cohort ($n = 9,691$) of Caucasian Herpes patients haplogroup H was protective (OR = 0.82;95 % CI = 0.71–0.94) whereas the IWX clade was a risk factor for herpes zoster status (OR = 1.38; 95 % CI = 1.07–1.77). In HIV infected patients haplogroup H was associated with a lower chance of developing AIDS and higher odds of having a better CD4 + recovery than patients without this haplogroup (Medrano et al., 2018; Guzmán-Fulgencio et al., 2013). Haplogroup R (16223C) and H (7028C) were associated with a significant protection against severe sepsis among Han Chinese and Europeans (Baudouin et al., 2005; Yang et al., 2008; Jiménez-Sousa et al., 2015). This sepsis-protective might confer a survival advantage for H-carriers, that could explain in part why H is the most common European haplogroup despite being the most recent.

In reference to COVID-19, to our knowledge only one study afforded the association with common mtDNA variants (Wu et al., 2021). In this Chinese based case-control study the authors concluded that mtDNA variants defining common haplogroups might contribute to individual's risk of developing severe COVID-19. This finding was in agreement with our results, but the data are difficult to compare because the different haplogroup profile between Chinese and European populations. Additional studies to characterise the whole mtDNA variation in individuals with the risk haplogroups should be necessary to determine whether these populations share particular functional variants that might explain the association with severe COVID-19.

5. Study limitations

Our study was based on a limited number of patients and from a single population, and requires validation in larger cohorts and from different regions. Also, the variants that defined the haplogroups were not functional and an explanation of the putative mechanism linking the mtDNA variants with severe COVID-19 is not provided, beyond the reported difference in mitochondrial function between the different haplogroups (Kenney et al., 2014; Kenney et al., 2014; Krzywanski et al., 2016). This would require a complete sequencing of the mtDNA in patients, as well as functional studies to determine the putative effect on the control of viral infection.

6. Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. An Excel file with the raw data would be available for meta-analysis research.

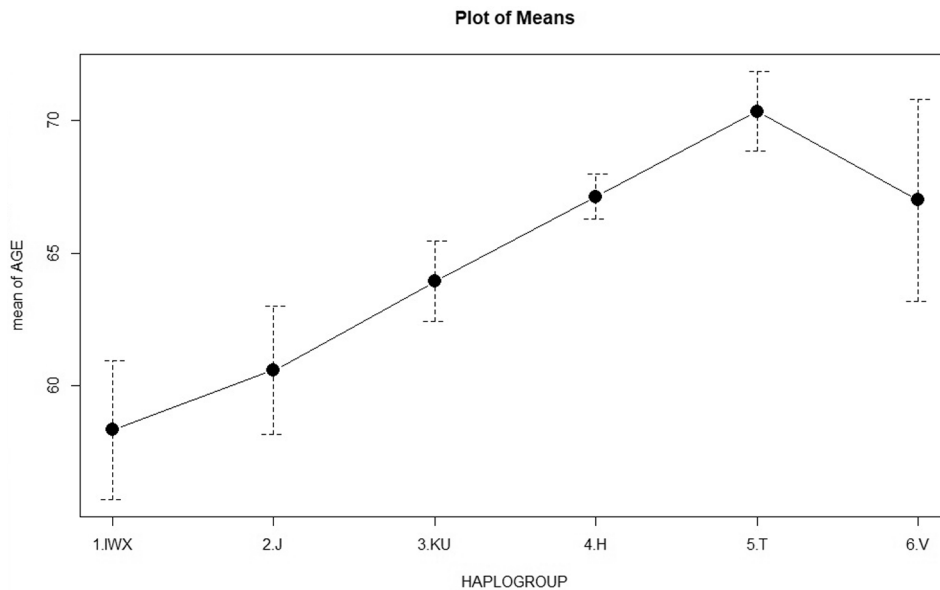


Fig. 2. Mean ages for the common haplogroups in the critical COVID-19 patients. Haplogroups IWX (16223T) had a significantly lower mean age compared to the other haplogroups (16223C): 58 vs 66 years, $p = 0.006$. The frequency of 16223T was significantly higher among early-onset (≤ 65 years) patients, $p = 0.03$. The frequency of 7028C (haplogroup H) was significantly lower among early-onset patients, $p = 0.002$.

7. Ethics and consent

This study was approved by the clinical research ethics committee of Hospital Universitario Central Asturias (HUCA). All the participants or they next of kin gave written or verbal consent. Data were handled in observance of Spanish legislation on data protection. The study complies with the principles of the Declaration of Helsinki (“Recommendations guiding doctors in biomedical research involving human subjects”).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mito.2022.09.001>.

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