article

Mitochondrial DNA haplogroup R predicts survival advantage in severe sepsis in the Han population

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Purpose: To determine whether the main mitochondrial DNA (mtDNA) haplogroups of the Han people have an impact on long-term clinical outcome. **Methods:** We prospectively studied 181 individuals who were sequentially admitted to the intensive care unit. Demographic and clinical data were recorded along with clinical outcome over 180 days. Follow-up was completed for all study participants. We then determined the mtDNA haplogroups of the patients and 570 healthy, age-matched Han people from Zhejiang province, Southeast China, by analyzing sequences of hypervariable mtDNA segments and testing diagnostic polymorphisms in the mtDNA coding region with DNA probes. **Result:** The frequency of the main subhaplogroups of the Han population in the study cohort did not differ significantly from the control group. mtDNA haplogroup R, one of the three main mtDNA haplogroups of the Han people, was a strong independent predictor for the outcome of severe sepsis, conferring a 4.68-fold (95% CI 1.903–10.844, $P = 0.001$) increased chance of survival at 180 days compared with those without the haplogroup R. **Conclusion:** In the Han population, mtDNA haplogroup R was a strong independent predictor for the outcome of severe sepsis, conferring an increased chance of long-term survival compared with individuals without the R haplogroup. ***Genet Med* 2008:10(3):187–192.**

Key Words: *mtDNA, haplogroup, severe sepsis*

Severe sepsis is defined as sepsis plus evidence of organ dysfunction,[1] and the development of sequential organ dysfunction is the most common cause of death in the intensive care unit.[2] The pathophysiology of organ dysfunction associated with sepsis is not yet clear, but likely involves multiple factors, such as microcirculatory dysfunction, disturbed tissue oxygenation, deranged apoptosis, and direct cytotoxicity of cytokines, and other sepsis-related compounds.[3] Recently, several studies have indicated that impaired cellular oxygen utilization, or "cytopathic hypoxia," might play an important role in the development of multiple organ dysfunction in severe sepsis.[4–6] Most cellular oxygen delivered to tissues is used by the mitochondria, which produce adenosine triphosphate (ATP), the main intracellular energy source needed for normal cellular function and metabolic homeostasis. ATP is produced by oxidative phosphorylation, a process conducted by a series of five enzyme complexes located on the inner mitochondrial membrane.[7] Accordingly, there is a strong likelihood that mitochondrial dysfunction contributes significantly to morbidity and mortality in the clinical setting during severe sepsis.

The mitochondrion contains multiple copies of a small circular genome of approximately 16,000 nucleotide base pairs, and this mitochondrial DNA (mtDNA) encodes for 13 peptides (subunits of Complexes I, III, and IV and the ATP synthase complex), 2 ribosomal ribonucleic acids (RNAs), and 22 transfer RNAs.[8] Human mtDNA is maternally inherited and the population can be divided into several mtDNA haplogroups on the basis of specific single nucleotide polymorphisms (SNPs) scattered throughout the mitochondrial genome.[9] A body of evidences suggested that mtDNA haplogroups have functional importance, being associated with respiratory-chain activity[10] and disease susceptibility, such as Alzheimer disease,[11] Parkinson disease,[12,13] and breast and esophageal cancer.[14] More recently, it has been reported that mtDNA haplogroup H, the most common subdivision of mtDNA in Europe, was a strong independent predictor of outcome during severe sepsis, conferring a 2.12-fold increased chance of survival at 180 days compared with individuals without the haplogroup H.[15] Although different populations have unique mtDNA haplogroup types, we hypothesized that a similar phenomena could occur in other ethnic groups beside Europeans. However, so far there has been no reported data.

The Han people constitute China's and the world's largest ethnic group, making up about 93% of the country's population and nearly 20% of all humankind. Most of the Han

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mtDNA can be allocated to specific subhaplogroups of Eurasian founder haplogroups M, N, and R (which is itself a subhaplogroup of N shared between Europe and East Asia).[16] In the present study, we prospectively studied a cohort of 181 patients with severe sepsis, to determine whether the main mtDNA haplogroups of the Han people have an impact on clinical outcome.

MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee of Zhejiang University and informed consent was obtained from guardians and/or patients.

The published frequencies of mtDNA haplogroups M, N, and R are 41.0, 47.9, and 37.3%, respectively in local Han people,[16] and our preliminary work showed similar haplogroup frequencies (data not shown). In accordance with the data about local haplogroup frequencies, the sample size was estimated based on an a priori power calculation indicating 80% power to detect a 2-fold difference in risk for haplogroup R (as this haplogroup has the lowest frequency) between nonsurvivors and survivors at the 0.05 significance level. One hundred eighty-one patients with severe sepsis were recruited sequentially on admission to the intensive care unit at the First Affiliated Hospital, College of Medicine, Zhejiang University, as defined by the diagnostic criteria published by the International Sepsis Definitions Conference.[1]

Acute physiology and chronic health evaluation (APACHE II) scores were documented at study entry and recorded daily, as were sepsis-related organ failure assessment (SOFA) scores until discharge from the intensive care unit or death, along with clinical outcome throughout 180 days. We used death during the 180-day period or survival at 180 days as endpoints. Follow-up was complete for all study patients.

Genomic DNA was extracted from whole blood samples of the study participants by the whole DNA extraction kit (Sangon, Shanghai, China). All DNA samples were stored at −20°C.

After clinical data were obtained, we determined mtDNA haplogroups. The sequence of the mtDNA hypervariable segment I (HSVI) from position 15996 to 16498 (relative to the revised Cambridge reference sequence (CRS)[17]) were amplified and sequenced. The primers used for polymerase chain reaction (PCR) were F-CTCCACCATTAGCACCCAAAGC and R- CCTGAAGTAGGAACCAGATG.

According to the preliminary typing determined by HSVI sequence analysis, we tested the specific polymorphisms used to define haplogroups in the mtDNA coding region. Eleven FAM-labeled oligonucleotide probes (Genecore, Shanghai, China) were designed to examine the diagnostic polymorphisms and are listed in Table 1. We performed PCR with fluorescence-labeled hybridization probes using a Master Mix Kit (ABI, Foster City, CA) on Mx3005P Real-time QPCR system (Stratagene, San Diego, CA). The sequence of mtDNA from position 8196 to 8316 was also amplified to evaluate a 9-bp deletion, which is the diagnostic marker for haplogroup B. The primers were F-ACAGTTTCATGCCCATCGTC and R-ATGCTAAGTTAGCTTTACAG.

Finally, comprehensive analysis of the HSVI sequences and diagnostic polymorphisms in mtDNA coding region identified the haplogroups, according to the updated East Asian mtDNA phylogenetic tree.[18]

The mtDNA haplogroup was also determined in 570 healthy, age-matched Han people from Zhejiang Province, Southeast China.

A univariate comparison was performed to compare variables between two groups using the unpaired *t* test for continuous variables and Fisher exact test for categorical variables. In all comparisons, $P < 0.05$ was considered statistically significant. Survival curves were estimated using the Kaplan–Meier method. Multivariate logistic regression analysis was applied to determine the independent contribution of mtDNA haplogroup to the prediction of the long-term outcome. The odds ratios with 95% confidence intervals (CI) were used to estimate the association between the independent variables and the dependent variable.

RESULTS

The baseline demographics and clinical characteristics of the patients are summarized in Table 2. The median age for patients with severe sepsis was 60 years, and 134 (74%) patients were male. The median APACHE II score on recruitment was 23.97 (IQR 20–34), and the median first 24 hours SOFA score was 8.28 (IQR 5–17). One hundred eleven (61.3%) individuals were discharged from the intensive care unit, 104 (57.5%) at hospital discharge, and 99 (54.7%) survived at 180 days. A univariate analysis indicated that survivors were significantly different from nonsurvivors for some demographic and clinical characteristics, including younger age, lower APACHE II, and SOFA scores, less likely to have chronic ill health (as defined in the APACHE II system), a lower occurrence of chest-related sepsis, and a higher occurrence of abdominal-related sepsis. However, gender and source of admission (whether surgical, medical, elective, or emergency), demonstrated no significance between the survivor and nonsurvivor cohorts (Table 2).

On admission to the intensive care unit, the frequency of the main subhaplogroups of the Han population in the study cohort did not differ significantly from the control group (Table 3). Fisher exact test indicated a higher 180-day survival rate in patients with mtDNA haplogroup R ($P = 0.006$, Table 4) compared with individuals without haplogroup R, and Kaplan–Meier analysis showed significantly higher survival over 180 days in patients with mtDNA haplogroup R than those without the haplogroup ($P = 0.0063$, Fig. 1). A comparison between demographic and clinical characteristics of the R and non-R haplogroup cohorts showed no significant differences (Table 2). To avoid the potential influence of some confounding risk factors, we subsequently did logistic regression analysis using 180-day survival as the independent variable and the following dependent variables: age, sex, APACHE II score and first 24

Table 1
The DNA primers and probes used to detect polymorphisms in the mtDNA coding region[a]

Haplogroups (DSNP)	Primers	Probes
F	F: CCTGGAGCCTCCGTAGACCTA	FAM-CCATCAATTTCATCACAAC
(6392)	R: GGGCGTTTGGTATTGGGTTA	
N9a	F: GATGAATAATAGCAGTTCTACCGTACAAC	FAM-CAGCACCACGACCCT
(5147)	R: AGCTTGTTTCAGGTGCGAGATAG	
Y	F: AACCCACACTCAACAGAAACAAAG	FAM-CTACAACCACGACCAAT
(14693)	R: GAGGTCGATGAATGAGTGGTTAATT	
A	F: GCTCACATCACCCCATAAACAAATA	FAM-TGGTCCTAGCCTTTC
(663)	R: GTGGTGATTTAGAGGGTGAACTCAC	
D	F: ACTACTCAACTTAAACTCCAGCACCAC	FAM-CCTGAAACAAGATAACATGAC
(5178A)	R: TGGGCAAAAAGCCGGTTAG	
G	F: CCTTTCACTTCTGAGTCCCAGA	FAM-CAAGGCACCCCTCT
(4833)	R: GGGGCTAGTTTTTGTCATGTGAG	
M7	F: CCCTTCACCATTTCCGACG	FAM-ACGGACTTCACGTCAT
(9824)	R: TGAAGCAGATAGTGAGGAAAGTTGA	
C	F: CATCAAAAAAATCGTAGCCTTCTC	FAM-CAAGTCAACTAGGACTC
(13263)	R: ACAGATGTGCAGGAATGCTAGGT	
Z	F: CGCAGACCTCCTCATTCTAACC	FAM-AGCTACCCTTTTACCATCA
(15784)	R: TTAGGATTGTTGTGAAGTATAGTACGGAT	
M8a	F: AACCGCATCCATAATCCTTCTAAT	FAM-TCCGGACAATGAA
(4715)	R: TTAATGATGAGTATTGATTGGTAGTATTGG	
M9	F: GCCCATACCCCGAAAATGT	FAM-CCCAACCCGTCATCTA
(4491)	R: GTGATGAGTGTGCCTGCAAAGA	

[a]The position of base alteration in degenerate oligonucleotide probes is underlined.
DSNP, diagnostic single nucleotide polymorphism; F, forward; R, reverse.

hours SOFA score, main source of sepsis, presence of chronic ill health, and the presence or absence of mtDNA haplogroup R. Higher APACHE II score (odds ratio 1.130, 95% CI 1.009–1.266, $P = 0.035$) and SOFA score (odds ratio 1.186, 95% CI 1.003–1.403, $P = 0.046$), and the presence of chronic ill health (odds ratio 3.499, 95% CI 1.581–7.741, $P = 0.002$) were independently associated with poor outcome. mtDNA haplogroup R was a strong independent predictor of outcome, conferring a 4.543-fold (95% CI 1.903–10.844, $P = 0.001$) increased chance of survival at 180 days compared with those without the haplogroup. Age ($P = 0.140$), sex ($P = 0.418$), and main source of sepsis ($P = 0.115$) were not independently associated with long-term outcome. To determine whether the survival advantage was restricted to a particular subhaplogroup of haplogroup R, we analyzed the two most common subhaplogroups of R—B and F— and found no significant difference in rates of survival between the two subhaplogroup cohorts ($P = 0.975$).

DISCUSSION

Sepsis is a polygenic and complex syndrome that is characterized by the development of multiple organ dysfunction after microbiologic invasion of the host. Genetic polymorphisms have been shown to be associated with the clinical outcomes in patients with severe infections. Most of these studies examined the genetic polymorphisms in essential genes, including Toll-like receptors, cytokines, and coagulation factors, and provided important insights into the mechanisms involved in the pathogenesis of sepsis-related organ dysfunction.[19] Mitochondria perform a variety of key cellular regulatory processes, such as ATP production, intracellular Ca^{2+} regulation, reactive oxygen species (ROS) generation and detoxification, and apoptosis,[20] and mitochondrial dysfunction contributes significantly to the pathogenesis of sepsis and multiple organ dysfunction.[6,21–23] Among mammalian organelles, the mitochondrion is unique, containing its own genome encoding 13 essential protein components of the mitochondrial respiratory chain.[8] It is well established in humans that the specific mtDNA polymorphisms create groups of related mtDNA haplogroups. Previous data of mtDNA variation have indicated that mtDNA haplogroups are linked with mitochondrial function.[10–14] Therefore, it is interesting to study whether mtDNA haplogroups are responsible for genetic variation in the clinical setting of sepsis. Baudouin et al.[15] have reported that mtDNA

Table 2
The demographic and clinical characteristics of the patients

	Total patients	Live cohort	Dead cohort	P^a	R cohort	Non-R cohort	P^b
Age (median)	60.05	54.20	67.11	<0.001	57.11	61.74	0.107
Male sex (%)	134 (74.0)	64 (64.6)	70 (78.0)	0.263	50 (75.8)	84 (75.2)	>0.999
Premorbidity (%)							
Cardiac failure	24 (12.3)	8 (8.1)	16 (19.5)	0.028	9 (13.6)	15 (13.0)	0.910
Ischemic heart disease	18 (9.9)	5 (5.1)	13 (15.9)	0.023	7 (10.6)	11 (9.6)	0.822
Liver disease	16 (8.8)	8 (8.1)	8 (9.8)	0.795	5 (7.6)	11 (9.6)	0.789
Pulmonary disease	35 (19.3)	16 (16.2)	19 (23.2)	0.260	16 (24.2)	21 (18.3)	0.347
Cancer	25 (13.8)	4 (4.0)	21 (25.6)	<0.001	5 (7.6)	20 (17.4)	0.076
Renal disease	20 (11.0)	7 (7.1)	13 (15.9)	0.094	9 (13.6)	11 (9.6)	0.463
Hematological disease	3 (1.7)	1 (1.0)	2 (2.4)	0.591	2 (3.0)	1 (0.9)	0.301
Recent surgery (%)							
Elective	35 (19.3)	19 (19.2)	16 (19.5)	>0.999	12 (18.2)	23 (20.0)	0.846
Emergency	31 (17.2)	17 (17.2)	14 (17.1)	>0.999	13 (19.7)	18 (15.7)	0.541
No surgery	115 (63.5)	63 (63.6)	52 (63.4)	>0.999	43 (65.2)	72 (62.6)	0.732
APACHE II (median)	23.87	22.47	25.55	<0.001	24.58	23.46	0.086
First 24 h SOFA score (median)	8.28	7.57	9.15	<0.001	8.68	8.05	0.142
Main source of infection (%)							
Chest	107 (59.1)	48 (48.5)	59 (72.0)	0.001	39 (59.1)	68 (59.1)	0.996
Abdomen	44 (24.3)	25 (25.3)	19 (23.2)	0.015	14 (21.2)	30 (26.1)	0.462
Bloodstream	6 (3.3)	4 (4.0)	2 (2.4)	0.691	2 (3.0)	4 (3.5)	>0.999
Others	24 (13.3)	22 (22.2)	2 (2.4)	<0.001	11 (16.7)	13 (11.3)	0.306

[a]*P* value: live cohort vs. dead cohort.
[b]*P* value: R cohort vs. non-R cohort.

Table 3
The frequencies of the main subhaplogroups of Han population of the study cohort and control group

Haplogroup	Control (%)	Patient (%)	*P*
B	101 (17.7)	31 (17.1)	0.855
F	101 (17.7)	35 (19.3)	0.622
R	211 (37.0)	66 (36.5)	0.893
N9	25 (4.4)	8 (4.4)	0.985
A	43 (7.5)	18 (9.9)	0.303
N	279 (48.9)	92 (50.8)	0.659
D	140 (24.6)	42 (23.2)	0.711
G	19 (3.3)	5 (2.8)	0.813
M7	51 (8.9)	21 (11.6)	0.291
M8	45 (7.9)	13 (7.2)	0.754
M9	17 (3.0)	4 (2.2)	0.796
M	272 (47.7)	85 (47.0)	0.859
Other	19 (3.3)	4 (2.2)	0.445
Total	570	181	

Table 4
A 180-day survival of patients with severe sepsis subdivided into the major Han mtDNA population

	Patient	Live (%)	*P*
B	31	21 (67.7)	0.109
F	35	24 (68.6)	0.066
R	66	45 (68.2)	0.006
N9	8	4 (50.0)	>0.999
A	18	6 (33.3)	0.079
N	92	55 (59.8)	0.162
D	42	20 (47.6)	0.293
G	5	3 (60.0)	>0.999
M7	21	9 (42.9)	0.246
M8	13	6 (46.2)	0.521
M9	4	4 (100)	0.127
M	85	42 (49.4)	0.231
Other	4	2 (50.5)	>0.999
Total	181	99 (54.7)	

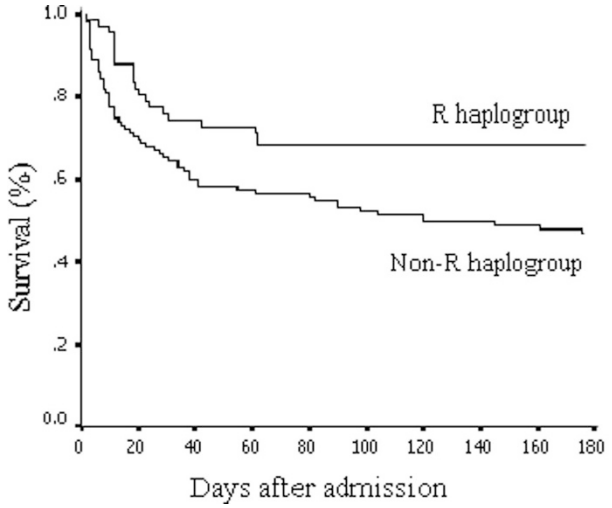

Fig. 1. Kaplan–Meier survival curve comparing the outcome of patients at 180 days after initial study entry ($P = 0.0063$).

haplogroup H, the most common subdivision of mtDNA in Europe, predicts better long-term outcome in patients with severe sepsis. Because various populations have unique mtDNA haplogroups, it is necessary to carry out similar investigations in different populations. Thus, we first performed such a clinical and genetic study in the Han people, Zhejiang province, Southeast China, and found one of the main subhaplogroups of Eurasian founder haplogroups, mtDNA haplogroup R, was the independent predictor for better long-term outcome in patients with severe sepsis.

It is known that the Han maternal gene pool largely belongs to three specific subhaplogroups of the Eurasian founder haplogroups, M, N, and R. In the Han population, mtDNA haplogroup R, which is itself a subhaplogroup of N shared between Europe and Asia, can be subdivided into two of the most common subgroups, F and B.[16] In addition, there is evidence to show that haplogroups F and B are the oldest of the Han mtDNA haplogroups and may have their diversification in Southern China and/or Southeast Asia, whereas other numbers of major subhaplogroups of M and N, including G, M8, M9, A and N9, may be of central or Northern Chinese provenance.[24,25] In accordance with the updated East Asian mtDNA phylogenetic tree, mtDNA haplogroup F can be identified by the specific polymorphisms at nucleotide 16304 in HSV I and nucleotide 6392 in the coding region, whereas mtDNA haplogroup B is defined by two polymorphisms at nucleotides 16189 and 16223, and its diagnostic marker, a 9-bp deletion. In the present study, we determined mtDNA haplogroups in 570 age-matched, healthy local Han people and found that the frequency of the major Han mtDNA haplogroups (B, F, A, N9, D, G, M7, M8, M9) is similar to the published data. Furthermore, there is no significant difference in the frequency between the controls and patients. This finding suggests that mtDNA haplogroups are not related to the development of sepsis, and highlights the representation of the study cohort in the general population. Our results are consistent with a previous study.[15]

Hitherto, studies of genetic variation in sepsis have focused on the nuclear DNA polymorphisms of the host immune system, although data about mtDNA haplogroups have been very limited, especially in the Asian population. As with the mtDNA haplogroup H in Europeans,[10] there is no direct evidence to show that mtDNA haplogroups are associated with mitochondrial function, especially respiratory-chain activity in the Asian population. However, the possibility should not be ignored. Our result, that the mtDNA haplogroup R confers a strong survival advantage, may provide potential insights into the relationship between mtDNA haplogroups and mitochondrial function. The specific polymorphisms used to define mtDNA haplogroup R, may suggest a possible explanation. Nucleotide 12705, the specific polymorphism site of mtDNA haplogroup R, lies within the mtDNA gene coding for the ND5, the subunit of Complex I. Mitochondrial complex I (NADH: ubiquinone oxidoreductase) catalyzes the electron transfer from NADH to ubiquinone.[26] Therefore, the 12705 polymorphism may influence the function of Complex I, such as electron transport, electron leakage, and ROS production. Other specific polymorphisms of mtDNA haplogroup R also have the similar characteristics, for instance, 3970 lying within the mtDNA gene coding for ND1, another subunit of complex I, 6392 lying within cytochrome oxidase subunit 1 coding region, and 9-bp deletion lying within the COII/$tRNA^{Lys}$ intergenic region. These polymorphisms all have the potential to alter mitochondrial function which plays a pivotal role in the pathogenesis of sepsis, thus impacting the clinical outcome. It is important to point out an alternative possibility that many different polymorphisms together may confer the effect on mitochondrial function rather than a single base difference. Further investigation should be performed to confirm these findings.

In summary, we prospectively studied a cohort of 181 patients with severe sepsis and found that mtDNA haplogroup R was a strong independent predictor for the outcome of severe sepsis, conferring a 4.68-fold increased chance of survival at 180 days compared with those without the haplogroup R. Our results provide potential insights into the relationship between mtDNA haplogroups and mitochondrial function, and a new prognosis predictor of severe sepsis.

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