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Association Between Mitochondrial DNA Haplogroup and Myelodysplastic Syndromes

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Abstract

Polymorphisms in mitochondrial DNA (mtDNA) are used to group individuals into haplogroups reflecting human global migration and are associated with multiple diseases, including cancer. Here, we evaluate the association between mtDNA haplogroup and risk of myelodysplastic syndromes (MDS). Cases were identified by the Minnesota Cancer Surveillance System (MCSS). Controls were identified through the Minnesota State driver's license/identification card list. Because haplogroup frequencies vary by race and ethnicity, we restricted analyses to non-Hispanic whites. We genotyped 15 mtSNPs that capture common European mitochondrial haplogroup variation. We used SAS v.9.3 (SAS Institute, Cary, NC) to calculate odds ratios (OR) and 95% confidence intervals (CI) overall and stratified by MDS subtype and IPSS-R risk category. We were able to classify 215 cases with confirmed MDS and 522 controls into one of the 11 common European haplogroups. Due to small sample sizes in some subgroups, we combined mt haplogroups into larger bins based on the haplogroup evolutionary tree, including HV (H+V), JT (J+T), IWX (I+W+X), UK (U+K), and Z for comparisons of cases and controls. Using haplogroup HV as the reference group, we found a statistically significant association between haplogroup JT and MDS (OR=0.58, 95% CI 0.36, 0.92, $P=0.02$). No statistically significant heterogeneity was observed in subgroup analyses. In this population-based study of MDS, we observed an association between mtDNA haplogroup JT and risk of MDS. While previously published studies provide biological plausibility for the observed association, further studies of the relationship between mtDNA variation and MDS are warranted in larger sample sizes.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of clonal hematologic disorders that result in dysplastic and ineffective hematopoiesis (Tefferi and Vardiman, 2009). Current data suggest that the incidence rates are 4.6 per 100,000 across all age groups in the United States, although several studies indicate that the true rate may be higher (Cogle et al., 2014). The etiology of MDS is not well understood, although age, male sex, smoking, obesity, prior chemotherapy and chemical and/or ionizing radiation exposures are known risk factors (Pedersen-Bjergaard et al., 2000; Strom et al., 2005; Ma et al., 2007; Rollison et al., 2008). Genetic susceptibility to MDS has not been widely evaluated to date.

While most mitochondrial DNA (mtDNA) was incorporated into human nuclear DNA throughout evolution, there remains a 16.6 kb closed double-stranded circular mt genome that contains 37 genes encoding 22 tRNAs, 2 rRNAs, and 13 proteins that play an integral role in OXPHOS (Anderson et al., 1981; Ballard and Whitlock, 2004). Because mitochondrial DNA (mtDNA) is inherited solely through the maternal line, it is a useful marker of human migration around the globe. Polymorphisms can be used to group individuals into haplogroups that reflect human global migration (van Oven and Kayser, 2009; Mitchell et al., 2014). These mitochondrial variants are associated with differences in mitochondrial function (Martinez-Redondo et al., 2010; Fernandez-Moreno et al., 2011; Gomez-Duran et al., 2012; Mueller et al., 2012; Kenney et al., 2013; Kenney et al., 2014) and have been associated with multiple diseases, including cancer (Singh and Kulawiec, 2009). One previous report in a Japanese population has suggested that mtDNA haplogroup M7b2 is associated with increased risk of hematopoietic cancer (Verma et al., 2007).

Given the importance of mitochondrial function in hematopoiesis (Norrdahl et al., 2011) and the presence of hematological alterations in mitochondrial disorders (Finsterer, 2007), we hypothesized that variation in mtDNA may influence risk of MDS. In this analysis, we evaluated the association between mtDNA haplogroup and risk of MDS, overall and by disease subtype and risk score. Because smoking is associated with MDS and is also known to influence mitochondria, we also conducted stratified analyses of mtDNA haplogroup and MDS in smokers and non-smokers.

MATERIALS AND METHODS

Study Population

Cases were identified by the Minnesota Cancer Surveillance System (MCSS), which is a population-based registry that collects information on all cancers diagnosed in Minnesota, using a rapid case ascertainment system. Pathology logs were typically received and reviewed by MCSS staff within 1–2 months of diagnosis. Cases were eligible for the study if they had a diagnosis of MDS (ICD-O-3 codes: 9980, 9982–9987, or 9989) between April 1, 2010 and October 31, 2014. Additional eligibility criteria included Minnesota residency, age at diagnosis between 20 and 85 years, and fluency in English or Spanish. Proxy interviews were not conducted. Centralized pathology and cytogenetics review were conducted to confirm diagnosis and classify by subtypes. Only cases with confirmed MDS following

independent reviews by two board-certified hematopathologists, a cytogeneticist, and a medical oncologist were included in the analysis.

Controls were identified through the Minnesota State driver's license/identification card list and were eligible if they were alive at the time of contact, resided in Minnesota, were between the ages of 20 and 85 years, could understand English or Spanish, and had no prior diagnosis of myeloid leukemia. Controls were frequency matched to cases on decile of age.

This study was approved by the Institutional Review Boards of the University of Minnesota, the Mayo Clinic, the Minnesota Department of Health and participating area hospitals.

DNA Extraction

Genomic DNA was collected from cases and controls using Oragene DNA collection kits (DNA Genotek, Ontario, Canada). DNA was extracted via Autopure LS Instrument according to manufacturer's instructions (Qiagen, Inc., Valencia, CA). DNA yield was quantified using a 1:10 dilution tested in triplicate by quantitative real-time PCR on an ABI Prism 7900HT Sequence Detection System using Sequence Detection Software v2.1 (Life Technologies, Grand Island, NY). Extracted DNA was stored at -20°C until further analysis.

mtDNA Genotyping

We selected 15 mtSNPs that capture common European mitochondrial haplogroup variation based on previous publications (Raby et al., 2007; Mitchell et al., 2014). mtSNPs were genotyped on the Sequenom iPLEX Gold MassArray platform (Sequenom, Inc., San Diego, CA) in the University of Minnesota Genomics Core. PCR and extension primers were designed using the MassARRAY Assay Design 3.0 software, and amplification and single base extension reactions were performed according to instructions (Tang et al., 1999, 2004). Extension product sizes were determined using Sequenom's Compact MALDI-TOF mass spectrometer. The resulting mass-spectra were converted to genotype data using SpectroTYPER-RT software.

Mitochondrial Haplogroup Classification

mtDNA SNPs were used to classify cases and controls into 11 common European haplogroups as described in previous publications (Raby et al., 2007; Mitchell et al., 2014). We were able to classify 97.4% of cases and 97.6% of controls into one of these haplogroups with frequency $> 1\%$ in our study population. Due to small sample sizes in some subgroups, we combined mt haplogroups into larger bins based on the haplogroup evolutionary tree, including HV (H+V), JT (J+T), IWX (I+W+X), UK (U+K), and Z (van Oven and Kayser, 2009) for comparisons of cases and controls.

Exposure Assessment

Exposure data were collected by a self-administered questionnaire that included demographics, anthropometrics, lifestyle factors including smoking, medical and family history, and occupational exposures. Smoking was categorized as ever/never use.

Statistical Analysis

All statistical analyses were conducted using SAS v.9.3 (SAS Institute, Cary, NC). Contingency table methods were used to compare categorical data. We estimated associations between haplogroup bins and MDS using multivariable logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Because haplogroup frequencies vary by race and ethnicity, we restricted comparisons between cases and controls to non-Hispanic whites. Polytomous logistic regression was used to evaluate associations by MDS subtype and IPSS-R risk category.

RESULTS

This analysis is based on an interim dataset of 237 non-Hispanic white cases deemed to have true MDS following centralized pathology review and 522 non-Hispanic white controls. Among cases, the median age at diagnosis was 74 years (range 35–91 years) and 66% were male. The controls followed a similar distribution due to the frequency matching by age and sex (median age 72 years, range 20–86 years; 67% male). The distribution of haplogroups in our control sample was similar to the distribution reported in a previous sample of non-Hispanic white individuals from the United States (Mitchell et al., 2014), with the highest number in the H haplogroup (42% in controls). Using haplogroup HV as the reference group, we found a statistically significant association between haplogroup JT and MDS (OR=0.58, 95% CI 0.36, 0.92, $P=0.02$; Table 1). No other significant associations were observed in a comparison of cases and controls.

In the analysis by MDS subtype (Table 2), the association with haplogroup JT reached statistical significance only in MDS cases with the RCMD subtype (OR=0.42, 95% CI 0.18, 0.99), although the association was similar in magnitude for RARS and the P -value for the test for heterogeneity was non-significant (0.77). Similarly, the associations between haplogroup JT and MDS were similar in magnitude in the model stratified by IPSS-R risk category (Table 3; P -value = 0.75).

When we stratified by smoking status, we saw similar associations in smokers and non-smokers for haplogroup JT (OR=0.64, 95% CI 0.33, 1.24 and OR=0.56, 95% CI 0.29, 1.09, respectively). The other haplogroup associations were also similar in magnitude to the analysis including all cases (data not shown).

DISCUSSION

In this analysis, we observed a reduced risk of MDS in individuals with mtDNA haplogroup JT. We did not observe heterogeneity by disease subtype or risk score, although power was limited for subgroup analyses. While mtDNA haplogroups are used to track human migration, they are not a perfect proxy for continental region of origin (Emery et al., 2015), suggesting that this association is not merely a proxy for ancestry. Mitochondrial damage accumulates during the normal aging process, including a decline in respiratory chain capacity, elevated oxidative damage, decreased mitochondrial content, and abnormalities in mitochondrial structure (Wang and Hekimi, 2015). MDS is primarily a disease of the elderly

(Ma et al., 2007; Rollison et al., 2008); therefore, it is plausible that mtDNA variation may play a role in etiology.

Variation in mitochondrial DNA has been hypothesized to play a role in the development of cancer due to the overlap in phenotypes associated with both mitochondrial defects and cancer, such as genome instability, resistance to apoptosis, and increased reactive oxygen species (Singh and Kulawiec, 2009). In fact, mitochondrial function has been known to be important in cancer cells since Otto Warburg made the observation that cancer cells undergo glycolysis even in the presence of oxygen (Warburg, 1956), termed the “Warburg effect” (Racker, 1972). Somatic mtDNA mutations are commonly found in cancer (Singh, 2004). Individuals with mitochondrial disease do not appear to be at increased risk of cancer (Lund et al., 2015); however, epidemiologic studies of cancer have provided mixed evidence for a role of inherited mtDNA variation and cancer risk. An increased risk of hematopoietic cancer was reported in individuals with the M7B2 haplogroup in the Japanese population in one previous study (OR=2.46, 95% CI 1.06, 5.73) (Singh and Kulawiec, 2009). To our knowledge, this is the first study to evaluate the association between MDS and mtDNA variation.

Previous studies using cybrid cells, which are cell lines consisting of identical nuclear DNA but containing mitochondria from different haplogroups, have reported functional differences by mtDNA haplogroup. For example, cybrids from haplogroup T demonstrate higher capacity to cope with oxidative stress (Mueller et al., 2012) while cybrids from haplogroup J exhibit lower levels of ATP and reactive oxygen species production (Kenney et al., 2013) in comparison with cybrids from haplogroup H. Further, altered expression of genes in the complement, inflammation, and apoptosis pathways was observed in J cybrids compared with H cybrids (Kenney et al., 2014).

Several population studies have also evaluated associations between health outcomes and mitochondrial haplogroups. Haplogroup JT has been associated with diverse phenotypes, including improved outcomes following a diagnosis of sepsis (Lorente et al., 2013, 2016), reduced risk of diminished ovarian reserve (May-Panloup et al., 2014), and reduced risk of Parkinson disease (Hudson et al., 2013). In one study of octo/nonagenarians, individuals with haplogroup J had lower systolic blood pressure and glutathione peroxidase activity (Rea et al., 2013). Finally, haplogroup J has been associated with longevity in multiple European populations (De Benedictis et al., 1999; Niemi et al., 2003). One intriguing possibility is that this association is mediated through telomere length. In fact, the one published study to date has reported longer telomere length in peripheral blood leukocytes of individuals with mtDNA haplogroup J compared with non-J carriers (Fernandez-Moreno et al., 2011). In aggregate, these data provide biological plausibility for the observed association although the specific mechanism will require further evaluation.

This study has a number of strengths, including the population-based design and the rigorous pathology, cytogenetics and clinical review. A number of limitations must also be considered. Given the poor outcomes associated with MDS (Ma et al., 2007), there is a potential for survival bias. While rapid case ascertainment was used to reduce this possibility, there is a possibility of bias if mtDNA haplogroup is associated with prognosis.

Selection bias is also possible given the response rates, although we observed no difference between cases and controls with respect to education or income. Given that MDS is a rare disease, our power was limited, especially for the subgroup analyses and the interaction analysis with smoking.

In summary, we observed an association between mtDNA haplogroup JT and risk of MDS in this population-based study of MDS. Previous studies using cybrid cells have reported functional differences by mtDNA haplogroup and provide biological plausibility for the observed association. Further studies of the relationship between mtDNA variation and MDS are warranted in larger sample sizes.

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TABLE 1

Association Between mtDNA Haplogroup Bins and MDS

Haplogroup	Controls N=522	MDS Cases N=237	OR ^a	95% CI	P-value
HV	233 (45)	118 (50)	Ref		
IWX	31 (6)	17 (7)	1.13	0.59–2.16	0.71
JT	115 (22)	37 (16)	0.58	0.36–0.92	0.02
UK	122 (23)	58 (24)	1.00	0.67–1.50	0.99
Z	21 (4)	7 (3)	0.67	0.26–1.71	0.40
<i>p-value</i>					0.15

CI, confidence interval; mtDNA, mitochondrial DNA; MDS, myelodysplastic syndromes; OR, odds ratio

^a Adjusted for sex and age at diagnosis (age as continuous variable)

TABLE 2

Association Between mtDNA Haplogroup and MDS by Disease Subtype

Haplogroup	Controls N=522	RCMD N ^a =68	OR (95% CI) ^b	RAEB-1 N ^a =43	OR (95% CI) ^b	RAEB-2 N ^a =41	OR (95% CI) ^b	RARS N ^a =35	OR (95% CI) ^b
HV	233 (45)	36 (53)	Ref	18 (42)	Ref	18 (44)	Ref	19 (54)	Ref
IWX	31 (6)	3 (4)	NC ^c	3 (7)	NC ^c	5 (12)	2.19 (0.75 – 6.35)	2 (6)	NC ^c
JT	115 (22)	11 (16)	0.42 (0.18 – 0.99)	7 (16)	0.76 (0.29 – 2.01)	6 (15)	0.72 (0.28 – 1.88)	6 (17)	0.53 (0.17 – 1.66)
UK	122(23)	16 (25)	0.93 (0.48 – 1.79)	14 (33)	1.69 (0.78 – 3.65)	11 (27)	1.13 (0.50 – 2.56)	6 (17)	0.74 (0.26 – 2.11)
Z	21 (4)	2 (3)	NC ^c	1 (2)	NC ^c	1	NC ^c	2 (6)	NC ^c

CI, confidence interval; mtDNA, mitochondrial DNA; MDS, myelodysplastic syndromes; NC, not calculated; OR, odds ratio; RAEB, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia.

^aN does not sum to total due to missing/other disease subtype

^bAdjusted for sex and age at diagnosis (age as continuous variable)

^cOR's and 95% CI were not calculated for categories with fewer than 5 cases

Type 3 Analysis of Effects: 12df P-value=0.77

TABLE 3

Association Between mtDNA Haplogroup and MDS by IPSS-R Risk Score

Haplogroup	Controls N=522	High/ Very High N ^a =72	OR (95% CI) ^b	Intermediate N ^a =43	OR (95% CI) ^b	Low/ Very Low N ^a =79	OR (95% CI) ^b
HV	233 (45)	33 (46)	Ref	24 (56)	Ref	41 (52)	Ref
IWX	31 (6)	5 (7)	1.14 (0.41 – 3.13)	4 (9)	NC ^c	5 (6)	0.91 (0.33 – 2.51)
JT	115 (22)	11 (15)	0.68 (0.33 – 1.40)	5 (12)	0.42 (0.16 – 1.15)	15 (19)	0.70 (0.37 – 1.36)
UK	122 (23)	22 (31)	1.30 (0.73 – 2.34)	10 (23)	0.88 (0.41 – 1.92)	15 (19)	0.78 (0.41 – 1.47)
Z	21 (4)	1 (1)	NC ^c	0	NC ^c	3 (4)	NC ^c

CI, confidence interval; mtDNA, mitochondrial DNA; MDS, myelodysplastic syndromes; NC, not calculated; OR, odds ratio

^aN does not sum to total due to missing/other disease subtype

^bAdjusted for sex, age at diagnosis (age as continuous variable)

^cOR's and 95% CI were not calculated for categories with fewer than 5 cases.

Type 3 Analysis of Effects: 20df P-value=0.75