

Mitochondrial haplogroups associated with susceptibility toward cancer

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Since mitochondria play pivotal roles in carcinogenesis and metabolism of cancer cells, we analyzed the correlation between cancers and mitochondrial haplogroups and single nucleotide polymorphisms (mtSNPs) in consecutive autopsies. The study population comprised 1503 autopsied cases (696 male, 807 female) at Tokyo Metropolitan Geriatric Hospital registered in the Internet-based database of Japanese single nucleotide polymorphisms for geriatric research (JG-SNP). Age at death was 78.9 ± 9.3 years, ranging from 48 to 102 years for males, and 81.8 ± 9.3 years, ranging from 46 to 104 years for females (http://www.tmgh.metro.tokyo.jp/jg-snp/english/E_top.html). The genotypes for 149 polymorphisms in the coding region of the mitochondrial genome were determined, and the haplotypes were classified into 30 haplogroups, i.e., F, B5, B4a, B4b, B4c, A, N9a, N9b, Y, M10+M11+M12, M7a, M7b2, M7c, M8+Z+C, G1, G2, M9, D5, D4a, D4b, D4d, D4e, D4g, D4h, D4j, D4k, D4l, D4m, and D4n. Among these haplogroups, we focused on 6 haplogroups (F, A, M7a, M7b2, D4a, and D4b) with prevalence > 5%. Multivariate logistic regression analysis was performed with adjustment for age, the prevalence of drinking, and that of smoking.

Among 1363 subjects whose data were available for presence or absence of cancer, age, gender, history of alcohol intake, history of smoking, and mitochondrial haplogroups, 819 subjects carried a pathologically confirmed cancer(s) at the time of autopsy. Multivariate logistic regression analysis revealed that the subjects with the haplogroup B5 tended to have a reduced risk for all cancer ($P = 0.0400$) with an odds ratio of 0.526 (95% CI 0.285-0.971). In contrast, the haplogroup D4b was significantly associated with an increased risk for malignant lymphoma ($P = 0.0071$) with an odds ratio of 2.425 (95% CI 1.272-4.622), and this haplogroup was possibly a risk for prostatic cancer ($P = 0.0358$) with an odds ratio of 3.082 (95% CI 1.387-6.849). The haplogroup D4a was significantly associated with an increased risk for biliary tract cancer ($P = 0.0057$) with an odds ratio of 3.082 (95% CI 1.387-6.849). Subjects with the haplogroup M7b2 tended to have an increased risk for colon cancer ($P = 0.0131$), having an odds ratio of 2.390 (95% CI 1.201-4.757). Subjects with haplogroup F tended to have an increased risk for acute leukemia ($P = 0.0222$) with odds ratio of 3.747 (95% CI 1.208-11.628).

Among mtSNPs with frequency > 5%, 5 mtSNPs were markedly associated with cancer. The mtSNP 4071C>T (ND1: syn), representing haplogroups M7b2 and M7c, was associated with all cancer ($P = 0.006$) with an odds ratio of 1.708 (95% CI 1.146-2.507). The mtSNP 15535C>T (Cytb: syn), representing haplogroup B4, was associated with all cancer ($P = 0.005$) with an odds ratio of 1.867 (95% CI 1.204-2.896). The mtSNP 4655G>A (ND2: syn), representing haplogroup A1a, was associated with breast cancer ($P = 0.004$) with an odds ratio of 3.474 (95% CI 1.479-8.162). The mtSNP 5231G>A (ND2: syn), representing haplogroup N9a, was associated with biliary tract cancer ($P = 0.005$) with an odds ratio of 3.380 (95% CI 1.448-7.888).

Haplogrouping for these mtSNPs may prove informative for predicting the genetic risk for various cancers in Japan. (mtSNPdb http://www.giib.or.jp/mtsnp/index_e.shtml)