J Hum Genet (2007) 52:680–685
DOI 10.1007/s10038-007-0171-0

ORIGINAL ARTICLE

Longevity-associated mitochondrial DNA 5178 C/A polymorphism and its interaction with cigarette consumption are associated with pulmonary function in middle-aged Japanese men

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Received: 17 April 2007 / Accepted: 14 June 2007 / Published online: 17 July 2007

Abstract Pulmonary function is a crucial factor associated with longevity. Mitochondrial DNA 5178 cytosine/adenine (Mt5178 C/A) polymorphism is reported to be associated with longevity in the Japanese population. We have previously reported that Mt5178 C/A polymorphism is widely associated with physiological and biochemical status. The objective of this study was to investigate whether Mt5178 C/A polymorphism is associated with pulmonary function. The subjects were 463 Japanese men (mean age ± SD 54.0 ± 7.6 years). Genotyping of Mt5178 C/A was performed by polymerase chain reaction-restriction fragment length polymorphism. A cross-sectional study of the relationship between genotype and spirometric data, namely forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), was conducted. Among younger subjects (age <55 years), FVC and FEV_1 were significantly higher for men with Mt5178A than for those with Mt5178C. Interaction between Mt5178 C/A polymorphism and smoking habits in FEV_1/FVC ratio was observed. Cigarette consumption (pack-years of smoking) was significantly and negatively associated with FEV_1/FVC ratio for men with Mt5178C. Among older subjects (age ≥55 years), FEV_1/FVC ratio was significantly lower for current smokers with Mt5178C than for never smokers with Mt5178C or for never smokers with Mt5178A. Mt5178 C/A polymorphism and its interaction with cigarette consumption may be associated with pulmonary function in Japanese men.

Keywords Gene–environment interaction · Habitual smoking · Longevity · Mitochondrial DNA · Polymorphism · Pulmonary function

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Introduction

Pulmonary function is associated with mortality (Hole et al. 1996; Schünemann et al. 2000) and longevity (Golgberg et al. 1996; Jedrychowski 1990). Changes in pulmonary function with aging, for example lower vital capacity and lower forced expiratory volume in 1 s (FEV_1), are, moreover, observed for healthy individuals (Enright 2003).

Mitochondrial DNA 5178 cytosine/adenine (Mt5178 C/A) polymorphism (also known as NADH dehydrogenase subunit 2237 leucine/methionine (ND2-237 Leu/Met) polymorphism) is reportedly associated with longevity in

the Japanese population (Tanaka et al. 1998). The frequency of the Mt5178A genotype, a genetic marker of mitochondrial haplogroup D, is significantly higher in Japanese centenarians than in the general population (Alexe et al. 2007; Tanaka et al. 1998) and it is reported that individuals with Mt5178A (mitochondrial haplogroup D) are less susceptible to lifestyle-related adult-onset diseases, for example hypertension (Kokaze et al. 2007), diabetes (Wang et al. 2001), metabolic syndrome (Tanaka et al. 2007), myocardial infarction (Mukae et al. 2003; Takagi et al. 2004), and cerebrovascular diseases (Ohkubo et al. 2002), than those with Mt5178C. Mt5178 C/A polymorphism is, moreover, also reported to be associated with blood pressure (Kokaze et al. 2004a, 2007), serum lipid levels (Kokaze et al. 2001, 2003a), fasting plasma glucose levels and glucose tolerance (Kokaze et al. 2005a), serum uric acid levels (Kokaze et al. 2006), intraocular pressure (Kokaze et al. 2004b), hematological data (Kokaze et al. 2005b), and serum protein fraction levels (Kokaze et al. 2002, 2003b), and its interaction with smoking habits is associated with serum triglyceride levels (Kokaze et al. 2003a), intraocular pressure (Kokaze et al. 2004b), red blood cell counts (Kokaze et al. 2005b), and serum protein fraction levels (Kokaze et al. 2003b). As far as we are aware, however, no information is available about the relationship between Mt5178 C/A polymorphism and respiratory function or about its interaction with smoking habits in respiratory function.

Considering the relationship between pulmonary function and longevity (Golgberg et al. 1996; Jedrychowski 1990), physiological differences in pulmonary function between the Mt5178C and Mt5178A genotypes are of interest both respirologically and gerontologically. We therefore investigated whether Mt5178 C/A polymorphism or its interaction with smoking habits is associated with pulmonary function.

Methods

Subjects

A total of 488 male volunteers were recruited among individuals visiting the Mito Red Cross Hospital for regular medical check-ups between 1999 and 2000 August. This study was conducted in accordance with the Declaration of Helsinki (revised in Edinburgh in 2000) and was approved by the Ethics Committee of Kyorin University School of Medicine. Written informed consent was obtained from all volunteers before participation. Among the volunteers, 25 men were excluded from analysis because they were diagnosed with respiratory diseases including COPD or because they had undergone abdominal surgery. The subjects were, therefore, 463 Japanese men (mean age ± SD 54.0 ± 7.6 years).

Clinical characteristics of subjects

Blood chemical and physical data, including spirometric data (forced vital capacity (FVC) and FEV_1), were determined as described previously (Kokaze et al. 2001). Percentage of predicted FVC (FVC%) and percentage of predicted FEV_1 (FEV_1%) are expressed using the predictive equation for the Japanese (Pulmonary Physiological Committee 1993). Smoking habits, including pack-years of smoking, were surveyed by means of a questionnaire. Smoking habits were classified into three categories—never, former, and current smokers.

Mt5178 C/A genotyping

Genotyping methods were as described previously (Kokaze et al. 2001). Briefly, DNA was extracted from white blood cells. Polymerase chain reaction-restriction fragment length polymorphism was performed using the restriction enzyme *Alu*I. The forward primer was 5′-CTTAGCATACTCCTCAATTACCC-3′ and the reverse primer was 5′-CTGAATTCTTCGATAATGGCCCA-3′. The absence of an *Alu*I site was designated as Mt5178A and the presence of this restriction site was designated as Mt5178C.

Statistical analysis

Statistical analyses were performed with SAS statistical software, version 8.2 for Windows (SAS Institute, Cary, NC, USA; 1999). In analysis of covariance (ANCOVA), Mt5178 C/A genotype (Mt5178C = 0, Mt5178A = 1) and smoking habits (never smokers = 0, former smokers = 1, current smokers = 2) were numerically coded. *P* values of less than 0.05 were considered statistically significant.

Results

In all subjects, FVC, FVC%, FEV_1, and FEV_1% were significantly higher for subjects with Mt5178A than for those with Mt5178C ($P = 0.028$, 0.049, 0.012, and 0.026, respectively) (Table 1). Among younger subjects (age <55 years), FVC, FVC%, FEV_1, and FEV_1% were significantly higher for subjects with Mt5178A than for those with Mt5178C ($P = 0.009$, 0.024, 0.008, and 0.023, respectively). Among older subjects, however, no statistical differences were observed in pulmonary function between the Mt5178C and Mt5178A genotypes.

Table 1 Characteristics of study subjects by Mt5178 C/A genotype

Total	Mt5178C (N = 282)	Mt5178A (N = 181)	P value
Age (years)	54.4 ± 7.5	53.3 ± 7.7	0.122
Height (cm)	167.8 ± 5.9	168.1 ± 6.2	0.568
Body mass index (kg m^{-2})	23.2 ± 2.8	23.5 ± 2.6	0.216
Never/former/current smokers (n)	89/80/113	65/43/73	0.469
Lifetime smoking (pack-years)	21.2 ± 20.4	21.0 ± 21.8	0.952
FVC (L)	3.68 ± 0.59	3.81 ± 0.64	0.028
FVC% (%)	92.9 ± 11.5	95.0 ± 11.6	0.049
FEV_1 (L)	3.13 ± 0.52	3.26 ± 0.54	0.012
FEV_1% (%)	93.7 ± 12.1	96.3 ± 11.5	0.026
FEV_1/FVC ratio (%)	85.0 ± 5.9	85.5 ± 6.0	0.440
Age <55	Mt5178C (N = 125)	Mt5178A (N = 93)	
Height (cm)	169.1 ± 6.1	170.3 ± 6.2	0.145
Body mass index (kg m^{-2})	23.2 ± 2.7	23.6 ± 2.5	0.261
Never/former/current smokers (n)	29/30/66	24/24/45	0.809
Lifetime smoking (pack-years)	22.0 ± 18.8	22.5 ± 20.3	0.840
FVC (L)	3.87 ± 0.61	4.09 ± 0.60	0.009
FVC% (%)	92.6 ± 11.7	96.2 ± 11.0	0.024
FEV_1 (L)	3.32 ± 0.51	3.51 ± 0.49	0.008
FEV_1% (%)	92.8 ± 11.1	96.2 ± 10.4	0.023
FEV_1/FVC ratio (%)	86.1 ± 6.3	86.0 ± 5.4	0.903
Age ≥55	Mt5178C (N = 157)	Mt5178A (N = 88)	
Height (cm)	166.8 ± 5.4	165.8 ± 5.2	0.177
Body mass index (kg m^{-2})	23.2 ± 2.9	23.4 ± 2.7	0.549
Never/former/current smokers (n)	60/50/47	41/18/29	0.152
Lifetime smoking (pack-years)	20.5 ± 21.7	19.5 ± 23.3	0.737
FVC (L)	3.53 ± 0.54	3.52 ± 0.53	0.836
FVC% (%)	93.1 ± 11.4	93.8 ± 12.1	0.622
FEV_1 (L)	2.98 ± 048	3.00 ± 0.46	0.762
FEV_1% (%)	94.5 ± 12.8	96.3 ± 12.6	0.277
FEV_1/FVC ratio (%)	84.6 ± 6.0	85.6 ± 5.5	0.206

Except for smoking habits, values are given as means ± SD. For frequency of smoking, P values were calculated by use of the chi-squared test. All P values depict significance of differences between Mt5178A and Mt5178C

ANCOVA showed that smoking habits (never smokers = 0, former smokers = 1, current smokers = 2), age, and height were significantly and negatively associated with FEV_1/FVC ratio ($P < 0.001$, $P < 0.001$, and $P = 0.048$, respectively). ANCOVA also revealed a gene–environment interaction between Mt5178 C/A polymorphism and smoking habits for FEV_1/FVC ratio ($P = 0.033$).

Simple and multiple linear regression analyses showed that cigarette consumption (pack-years of smoking) was significantly and negatively associated with FEV_1/FVC ratio in men with Mt5178C (simple linear regression analysis $P < 0.001$ and multiple linear regression analysis $P < 0.001$, respectively) (Table 2). Age was also significantly and negatively associated with FEV_1/FVC ratio in men with Mt5178C (simple linear regression analysis $P = 0.007$ and multiple linear regression analysis $P = 0.004$, respectively).

Bonferroni correction for multiple comparisons showed that FEV_1/FVC ratio was significantly lower for current smokers with Mt5178C than for never smokers with Mt5178C and never smokers with Mt5178A ($P < 0.001$ and $P < 0.001$, respectively; Table 3). FEV_1/FVC ratio was, moreover, significantly lower for former smokers with Mt5178A than for never smokers with Mt5178A ($P = 0.047$). Among older subjects (age ≥55 years), FEV_1/FVC ratio was significantly lower for current smokers with Mt5178C than for never smokers with Mt5178C and never smokers with Mt5178A ($P < 0.001$ and $P = 0.001$,

Table 2 Simple and multiple linear regression analyses for FEV1/FVC ratio between Mt5178C and Mt5178A genotypes

	Mt5178C			Mt5178A		
	Regression coefficient	SEM	*P* value	Regression coefficient	SEM	*P* value
Simple linear regression analysis						
Pack-years	–0.077	0.018	<0.001	–0.034	0.019	0.070
Age (years)	–0.133	0.049	0.007	–0.035	0.053	0.504
Height (cm)	–0.036	0.063	0.570	–0.070	0.067	0.297
	Mt5178C			Mt5178A		
	Partial regression coefficient	SEM	*P* value	Partial regression coefficient	SEM	*P* value
Multiple linear regression analysis						
Pack-years	–0.076	0.017	<0.001	–0.031	0.019	0.101
Age (years)	–0.143	0.049	0.004	–0.075	0.060	0.209
Height (cm)	–0.082	0.062	0.187	–0.101	0.076	0.187

Table 3 Comparison of FEV1/FVC ratio (%) by Mt5178 C/A genotype and smoking status

Total	Mt5178C			Mt5178A		
	Never smokers (*N* = 89)	Former smokers (*N* = 80)	Current smokers (*N* = 113)	Never smokers (*N* = 24)	Former smokers (*N* = 24)	Current smokers (*N* = 45)
FEV_1/FVC ratio (%)	87.0 ± 0.6**	86.0 ± 0.6	83.5 ± 0.5	87.4 ± 0.7**†	84.0 ± 0.9	85.2 ± 0.7
Age <55	Mt5178C			Mt5178A		
	Never smokers (*N* = 29)	Former smokers (*N* = 30)	Current smokers (*N* = 66)	Never smokers (*N* = 24)	Former smokers (*N* = 24)	Current smokers (*N* = 45)
FEV_1/FVC ratio (%)	87.1 ± 1.1	87.6 ± 1.1	84.9 ± 0.7	87.8 ± 1.2	85.0 ± 1.2	85.5 ± 0.9
Age ≥55	Mt5178C			Mt5178A		
	Never smokers (*N* = 60)	Former smokers (*N* = 50)	Current smokers (*N* = 47)	Never smokers (*N* = 41)	Former smokers (*N* = 18)	Current smokers (*N* = 29)
FEV_1/FVC ratio (%)	86.6 ± 0.7**	84.7 ± 0.8	82.0 ± 0.8	86.9 ± 0.9*	83.1 ± 1.3	85.2 ± 1.0

FEV_1/FVC ratios (%) are given as means ± SEM. The Bonferroni correction for multiple comparisons was applied. *$P < 0.005$ and **$P < 0.001$ compared with current smokers with Mt5178C. †$P < 0.05$ compared with former smokers with Mt5178A

respectively). Among younger subjects (age <55 years), however, no significant differences were observed in FEV_1/FVC ratio between Mt5178C genotype and Mt5178A genotype.

Discussion

These results reveal that Mt5178 C/A polymorphism and its interaction with smoking habits may be associated with respiratory function in Japanese men. Among younger subjects (age <55 years), FVC, FVC%, FEV_1, and FEV_1% were significantly higher for men with Mt5178A than for those with Mt5178C. A gene–environment interaction between Mt5178 C/A polymorphism and smoking habits in FEV_1/FVC ratio was observed. Cigarette consumption and age were significantly and negatively associated with FEV_1/FVC ratio in subjects with Mt5178C. Among older subjects (age ≥55 years), FEV_1/FVC ratio was significantly lower for current smokers with Mt5178C than for never smokers with Mt5178C. There was, however, no statistically significant difference in FEV_1/FVC ratio between current smokers and never smokers with Mt5178A.

Japanese women with mitochondrial haplogroup A are susceptible to atherothrombotic cerebral infarction (Nishigaki et al. 2007). Conversely, mitochondrial haplogroup N9a is associated with resistance to metabolic syndrome (Tanaka et al. 2007) or type 2 diabetes (Fuku et al. 2007)

and is a protective factor against myocardial infarction (Nishigaki et al. 2006). Individuals with mitochondrial haplogroup D (Mt5178A genotype) also seem to resist adult-onset atherosclerotic diseases (Mukae et al. 2003; Takagi et al. 2004; Ohkubo et al. 2002) and tend to experience increased longevity. Goldberg et al. (1996) pointed out that higher FVC was one of the factors associated with longevity. Jedrychowski (1990) also reported that FVC and FEV_1 are significantly higher for elderly men with long-lived parents than for those with shorter-lived parents. In addition to antiatherogenic properties, higher FVC and higher FEV_1 in middle age are probably biophysical factors associated with longevity in individuals with the Mt5178A genotype (mitochondrial haplogroup D).

We have discovered gene–environment interactions between Mt5178 C/A polymorphism and smoking habits for serum triglyceride levels (Kokaze et al. 2003a), intraocular pressure (Kokaze et al. 2004b), hematological data (Kokaze et al. 2005b), serum protein fraction levels (Kokaze et al. 2003b), and, in this study, FEV_1/FVC ratio. The precise mechanisms through which Mt5178 C/A polymorphism exerts its interaction with habitual smoking, and thereby affects biophysical and biochemical status, are unknown. Cigarette smoking-generated reactive oxygen species (ROS) attack mitochondria (Banzet et al. 1999) and attenuate activity of NADH dehydrogenase (Smith et al. 1993). Because methionine residues act as an endogenous antioxidant (Levine et al. 1996), the amino acid change from leucine to methionine at residue 237 of NADH dehydrogenase subunit 2 may bring about biophysical and biochemical changes, for example altering sensitivity or resistance to ROS. It is thought that differences in enzymatic function and sensitivity to ROS between ND2-237Leu (Mt5178C) and ND2-237Met (Mt5178A) result in differences in biophysical and biochemical status, including pulmonary function. Stevenson et al. hypothesized that smokers susceptible to developing COPD have a genetic disadvantage that results in an attenuated aerobic capacity, antioxidant defense deficiencies, and mitochondrial dysfunction (Stevenson et al. 2006). Interaction between Mt5178 C/A polymorphism and habitual smoking in respiratory function apparently support their hypothesis, although further investigation of the differences in ROS-caused pulmonary dysfunction between the Mt5178A and Mt5178C genotypes is required.

Considering other genetic polymorphisms associated with pulmonary function (Nakamura et al. 2006) or risk of COPD (Hegab et al. 2004; Ito et al. 2004) in the Japanese population, gene–gene or gene–gene–environment interactions in respiratory function should be investigated. Our findings show that cigarette consumption increases the risk of COPD in Mt5178C genotypic men. Because patients with COPD were excluded from this study, however, a well-designed case-control study is required to clinically evaluate the interaction between Mt5178 C/A polymorphism and smoking habits on risk of COPD.

In conclusion, longevity-associated Mt5178 C/A polymorphism and its interaction with cigarette consumption may be associated with pulmonary function in Japanese men. Higher FVC and higher FEV_1 in middle age may be a biophysical factor associated with longevity in Mt5178A genotypic men. Smoking-related decreases in FEV_1/FVC ratio may be more evident for men with Mt5178C than for those with Mt5178A. These findings may therefore contribute to elucidating the gerontological significance of relationships between mitochondrial function, pulmonary function, and longevity, and may clinically assist in establishing personalized prevention for pulmonary dysfunction and personalized guidance for smoking cessation on the basis of genetic information.

Acknowledgments This study was supported in part by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 14570355 and No. 18590572) and the Chiyoda Mutual Life Foundation.

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