Table 2 Clinical characteristics of study participants according to the genotypes of *UCP2* or *UCP3* polymorphisms

	UCP2 45 bp I/D genotype			*P*			*UCP3* −55 C/T genotype			*P*		
Characteristics	D/D	I/D	I/I	Codominant	Dominant	Recessive	C/C	C/T	T/T	Codominant	Dominant	Recessive
Number	163	77	14				118	116	21			
Age (years)	21.4 ± 0.2	21.7 ± 0.3	21.9 ± 0.7	0.506	0.259	0.514	21.7 ± 0.2	21.4 ± 0.2	21.5 ± 0.5	0.703	0.405	0.904
Height (cm)	172.0 ± 0.4	173.2 ± 0.6	172.3 ± 1.2	0.317	0.159	0.938	172.5 ± 0.5	172.0 ± 0.5	173.7 ± 1.3	0.390	0.740	0.235
Body weight (kg)	62.3 ± 0.6	63.2 ± 1.0	62.0 ± 2.2	0.725	0.522	0.802	63.6 ± 0.8	61.4 ± 0.7	62.5 ± 1.6	0.142	0.056	0.969
BMI (kg/m^2)	21.0 ± 0.2	21.0 ± 0.3	20.9 ± 0.8	0.990	0.955	0.884	21.4 ± 0.2	20.7 ± 0.2	20.7 ± 0.4	0.116	**0.038**	0.482
SBP (mmHg)	110.3 ± 0.7	111.7 ± 1.1	117.3 ± 2.9	**0.014**	0.051	**0.007**	112.3 ± 1.0	110.1 ± 0.8	110.7 ± 2.2	0.201	0.079	0.829
DBP (mmHg)	62.4 ± 0.7	63.3 ± 1.2	66.6 ± 1.3	0.166	0.193	0.080	64.0 ± 0.8	62.4 ± 0.8	61.2 ± 1.6	0.238	0.110	0.317
MBP (mmHg)	78.4 ± 0.6	79.5 ± 1.1	83.5 ± 1.6	**0.038**	0.082	**0.017**	80.1 ± 0.8	78.3 ± 0.7	77.7 ± 1.6	0.164	0.060	0.401
HR (supine rest, bpm)	61.3 ± 0.7 (n = 160)	61.1 ± 0.9 (n = 76)	57.8 ± 2.4 (n = 14)	0.363	0.536	0.157	61.3 ± 0.8 (n = 115)	60.7 ± 0.9 (n = 115)	60.8 ± 1.9 (n = 21)	0.876	0.608	0.923
HR (standing, bpm)	82.2 ± 0.9 (n = 156)	80.4 ± 1.1 (n = 73)	78.1 ± 2.7 (n = 14)	0.231	0.125	0.219	81.5 ± 0.9 (n = 115)	80.8 ± 1.1 (n = 111)	84.2 ± 1.6 (n = 18)	0.442	0.871	0.238
Family history of HT, DM, or obesity (%)	22.7	33.8	42.9	0.079	**0.032**	0.175	33.1	20.7	28.6	0.103	**0.046**	0.871

Values are mean ± SEM and were compared by one-way ANOVA or Student's *t*-test. Chi-square test was performed for analysis of genotype distributions as to family history. *P* values of less than 0.05 are shown in boldface type. ANOVA, analysis of variance; bpm, beats per minute; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, heart rate; HT, hypertension; MBP, mean blood pressure; SBP, systolic blood pressure; SEM, standard error of mean.

Table 3 Power spectral parameters of heart rate variability according to the genotypes of *UCP2* 45 bp insertion/deletion polymorphism

	UCP2 45 bp I/D genotype			*P*			Adjusted *P*		
Parameters	D/D	I/D	I/I	Codominant	Dominant	Recessive	Codominant	Dominant	Recessive
Supine rest									
Number	160	76	14						
LF, ln ms^2 (geometric mean)	6.43 ± 0.07 (618.7)	6.25 ± 0.12 (517.6)	6.72 ± 0.30 (828.7)	0.179	0.412	0.191	0.172	0.325	0.230
LF (%)	56.6 ± 1.3	52.6 ± 2.0	63.6 ± 3.7	**0.041**	0.295	0.067	**0.038**	0.207	0.089
HF, ln ms^2 (geometric mean)	6.14 ± 0.08 (462.0)	6.13 ± 0.11 (459.5)	6.10 ± 0.29 (447.0)	0.992	0.936	0.905	0.992	0.931	0.907
HF (%)	43.4 ± 1.3	47.4 ± 2.0	36.4 ± 3.7	**0.041**	0.295	0.067	**0.038**	0.207	0.089
LF/HF, ln (geometric mean)	0.29 ± 0.06 (1.34)	0.12 ± 0.09 (1.13)	0.62 ± 0.17 (1.85)	**0.039**	0.323	0.059	**0.037**	0.228	0.078
Standing									
Number	156	73	14						
LF, ln ms^2 (geometric mean)	6.26 ± 0.06 (523.2)	6.18 ± 0.08 (484.6)	6.49 ± 0.15 (659.3)	0.332	0.779	0.199	0.333	0.624	0.243
LF (%)	83.9 ± 1.0	85.6 ± 1.0	90.0 ± 1.0	0.090	0.089	0.062	0.131	0.121	0.085
HF, ln ms^2 (geometric mean)	4.38 ± 0.08 (79.8)	4.25 ± 0.09 (70.3)	4.23 ± 0.18 (68.6)	0.565	0.286	0.660	0.553	0.262	0.673
HF (%)	16.1 ± 1.0	14.4 ± 1.0	10.0 ± 1.0	0.090	0.089	0.062	0.131	0.121	0.085
LF/HF, ln (geometric mean)	1.88 ± 0.07 (6.59)	1.93 ± 0.08 (6.89)	2.26 ± 0.11 (9.61)	0.218	0.330	0.091	0.278	0.401	0.119

LF (%) and HF (%) indicate percentage of LF or HF power in the range between 0.035 and 0.05 Hz (see methods for details). LF/HF indicates ratio of LF to HF power. Values are mean ± SEM; geometric means are given between parentheses. *P* values were obtained by one-way ANOVA or Student's *t*-test. Adjusted *P* values were calculated after adjusting for age, BMI, and family history of hypertension, diabetes, or obesity. *P* values <0.05 are shown in boldface type. ANOVA, analysis of variance; HF, high frequency; I/D, insertion/deletion; LF, low frequency; SEM, standard error of mean.

Table 4 Power spectral parameters of heart rate variability according to the genotypes of *UCP3* −55C/T polymorphism

Parameters	*UCP3* −55C/T genotype			*P*			Adjusted *P*		
	C/C	C/T	T/T	Codominant	Dominant	Recessive	Codominant	Dominant	Recessive
Supine rest									
Number	115	115	21						
LF, ln ms^2 (geometric mean)	6.45 ± 0.10 (635.9)	6.31 ± 0.09 (551.3)	6.50 ± 0.21 (663.4)	0.473	0.354	0.608	0.530	0.398	0.629
LF (%)	57.3 ± 1.5	54.5 ± 1.6	55.1 ± 3.3	0.419	0.191	0.839	0.408	0.182	0.792
HF, ln ms^2 (geometric mean)	6.13 ± 0.09 (459.3)	6.11 ± 0.08 (451.9)	6.27 ± 0.20 (530.3)	0.777	0.945	0.484	0.775	0.870	0.475
HF (%)	42.7 ± 1.5	45.5 ± 1.6	44.9 ± 3.3	0.419	0.191	0.839	0.408	0.182	0.792
LF/HF, ln (geometric mean)	0.33 ± 0.07 (1.38)	0.20 ± 0.07 (1.22)	0.22 ± 0.15 (1.25)	0.415	0.187	0.820	0.402	0.178	0.773
Standing									
Number	115	111	18						
LF, ln ms^2 (geometric mean)	6.26 ± 0.07	6.22 ± 0.07 (502.2)	6.40 ± 0.16 (604.7)	0.592	0.872	0.351	0.659	0.935	0.369
LF (%)	86.9 ± 0.8	82.5 ± 1.2	85.1 ± 1.7	**0.009**	**0.003**	0.916	**0.007**	**0.002**	0.974
HF, ln ms^2 (geometric mean)	4.19 ± 0.08 (66.1)	4.44 ± 0.09 (84.5)	4.56 ± 0.15 (95.3)	0.069	**0.024**	0.271	**0.034**	**0.011**	0.236
HF (%)	13.1 ± 0.8	17.5 ± 1.2	14.9 ± 1.7	**0.009**	**0.003**	0.916	**0.007**	**0.002**	0.974
LF/HF, ln (geometric mean)	2.07 ± 0.07 (7.91)	1.78 ± 0.08 (5.94)	1.85 ± 0.13 (6.35)	**0.022**	**0.006**	0.679	**0.016**	**0.004**	0.590

LF (%) and HF (%) indicate percentage of LF or HF power in the range between 0.035 and 0.05 Hz (see methods for details). LF/HF indicates ratio of LF to HF power. Values are mean ± SEM; geometric means are given between parentheses. *P* values were obtained by one-way ANOVA or Student's *t*-test. Adjusted *P* values were calculated after adjusting for age, BMI, and family history of hypertension, diabetes, or obesity. *P* values of less than 0.05 are shown in boldface type. ANOVA, analysis of variance; HF, high frequency; LF, low frequency; SEM, standard error of mean.

contrary, both low frequency percentage and low frequency/high frequency of the −55T allele carriers were significantly lower than those of the C/C carriers. These results suggested that the −55T allele was associated with a relatively lower sympathetic and a higher parasympathetic activity upon postural change to standing. These differences remained significant after adjustment for age, BMI, and family history of hypertension, diabetes, or obesity.

Combined effects of UCP2 and UCP3 polymorphisms

Modest linkage disequilibrium was seen between the *UCP2* 45 bp insertion/deletion and the *UCP3* −55C/T polymorphisms ($|D'| = 0.74$). Table 5 shows the combined effects of both polymorphisms on clinical characteristics. The comparison was conducted among four combined *UCP2–UCP3* genotype groups according to participants being with or without the *UCP2* 45 bp I allele or the *UCP3* −55 T allele (I allele + C/C, I allele + T allele, D/D + C/C, D/D + T allele). No significant interaction of *UCP2* and *UCP3* polymorphisms with BMI and BP was found. However, carriers of the *UCP2* 45 bp I allele–*UCP3* −55C/C combined genotype had the highest family history of hypertension, diabetes, and obesity among the combined genotype groups. On the other hand, some HRV parameters were significantly different between the groups (Table 6). In a standing position, carriers of the *UCP2* 45 bp D/D–*UCP3* −55T allele had the lowest sympathetic indices (low frequency percentage and low frequency/high frequency), with an accompanying increased parasympathetic index (high frequency percentage), suggesting that *UCP2* and *UCP3* polymorphisms have an additive effect on HRV.

Discussion

In the present study, in young Japanese men, we found a significant association of the *UCP2* 45 bp insertion/deletion or the *UCP3* −55C/T polymorphisms with HRV, indicating the contribution of both *UCP* polymorphisms to cardiac autonomic regulation. Autonomic imbalances are significantly involved in the pathophysiology of metabolic syndrome, CVD, and hypertension [43,44]. Previous studies have shown a sympathetic predominance reflected in increased HRV sympathetic indices (low frequency percentage or low frequency/high frequency) or reduced HRV parasympathetic indices (high frequency or high frequency percentage) in patients with hypertension or CVD [25–28]. In this context, pharmacological interventions (beta-blocker treatment) in patients with cardiac diseases have been shown to improve cardiac autonomic balance in which HRV sympathetic indices were reduced [45,46]. In the present study, participants carrying the *UCP3* −55T allele showed lower HRV sympathetic indices and higher HRV parasympathetic indices than carriers of the C/C genotype in a standing position, which was independent of age, BMI, and the family history of hypertension,

Table 5 Association of combined *UCP2–UCP3* genotypes with clinical characteristics

Characteristics	*UCP2–UCP3* combined genotypes				*P*
	D/D–T allele	D/D–C/C	I allele–T allele	I allele–C/C	
Number	98	65	39	52	
Age (years)	21.4 ± 0.2	21.5 ± 0.3	21.6 ± 0.4	21.9 ± 0.3	0.604
BMI (kg/m^2)	20.9 ± 0.2	21.3 ± 0.3	20.4 ± 0.3	21.5 ± 0.4	0.118
SBP (mmHg)	109.7 ± 0.9	111.1 ± 1.4	111.3 ± 1.6	113.9 ± 1.4	0.103
DBP (mmHg)	61.6 ± 0.7	63.7 ± 1.2	63.6 ± 1.8	64.3 ± 1.2	0.277
MBP (mmHg)	77.6 ± 0.7	79.5 ± 1.1	79.5 ± 1.6	80.8 ± 1.2	0.132
Family history of HT, DM, or obesity (%)	20.4	26.2	25.6	42.3	**0.039**

Values are mean ± SEM and were compared by one-way ANOVA. Chi-square test was performed for analysis of genotype distributions as to family history. *P* values of less than 0.05 are shown in boldface type. ANOVA, analysis of variance; DBP, diastolic blood pressure; DM, diabetes mellitus; HT, hypertension; MBP, mean blood pressure; SBP, systolic blood pressure; SEM, standard error of mean.

diabetes, and obesity. For the 45 bp insertion/deletion polymorphism of *UCP2*, the 45 bp I/I genotype was associated with relatively higher BP and HRV sympathetic indices at supine rest. These findings suggest that the studied *UCP* polymorphisms are associated with sympathovagal balance in resting or sympathetic activated (standing) conditions.

ROS-induced autonomic dysregulation can be related to hypertension, cardiac diseases, and neuropathy [10,11, 47–49]. Apart from roles in energy metabolism [1,2], UCP2 and UCP3 play an important role in the prevention of mitochondrial ROS formation [3,4] and have been implicated in the pathophysiology of hypertension and CVD [50–53]. Recent studies also suggest that ROS is closely related to ANS activity, with, for instance, a sympathoexcitation effect of ROS at the central, cardiac, and peripheral levels [10,11]. UCP families are expressed in various human tissues, including the CNS and dorsal root ganglion [8,9]. UCP3 has been shown to protect neurons from glucose-induced neuronal oxidative stress [9], whereas UCP2 exhibits both neuromodulatory and neuroprotective roles in the CNS [8,54].

Previous reports have shown increased UCP3 mRNA levels in the skeletal muscle in *UCP3* −55T allele carriers [18]; speculatively, the higher expression of *UCP3* in the −55T allele carriers may prevent or reduce oxidative stress in the ANS, which may protect from excessive cardiac sympathetic activation. On the other hand, UCP2 also plays a crucial role in decreasing ROS formation, which can affect BP or cardiovascular regulation [50–53]. Thus, the *UCP2* polymorphism may affect BP regulation through ROS or autonomic nervous modulation. In this context, significant associations between the *UCP2* −866G/A polymorphism, which was in linkage disequilibrium with the 45 bp insertion/deletion polymorphism [55], and hypertension [56], coronary artery disease [57], and oxidative stress [58] have been reported. However, in the present study, carriers of the 45 bp I/I genotype were limited because of the low abundance of the 45 bp I allele. Further large-scale studies are required to detect the precise impact of this polymorphism on BP variation.

Recent data suggest that UCP2 and UCP3 might be associated with obesity or obesity-related phenotypes. In the present study, carriers of the *UCP3* −55T allele

Table 6 Association of combined *UCP2–UCP3* genotypes with power spectral parameters of heart rate variability

Parameters	*UCP2–UCP3* combined genotypes				*P*	Adjusted *P*
	D/D–T allele	D/D–C/C	I allele–T allele	I allele–C/C		
Supine rest						
Number	98	62	38	52		
LF, ln ms^2 (geometric mean)	6.35 ± 0.09 (574.2)	6.55 ± 0.11 (696.2)	6.31 ± 0.15 (549.6)	6.33 ± 0.16 (562.3)	0.539	0.510
LF (%)	55.2 ± 1.6	58.8 ± 2.0	52.9 ± 3.0	55.4 ± 2.3	0.335	0.265
HF, ln ms^2 (geometric mean)	6.12 ± 0.10 (455.7)	6.16 ± 0.12 (472.0)	6.18 ± 0.12 (483.0)	6.09 ± 0.15 (439.8)	0.996	0.948
HF (%)	44.8 ± 1.6	41.2 ± 2.0	47.1 ± 3.0	44.6 ± 2.3	0.335	0.265
LF/HF, ln (geometric mean)	0.23 ± 0.07 (1.26)	0.39 ± 0.09 (1.47)	0.13 ± 0.13 (1.14)	0.25 ± 0.10 (1.28)	0.351	0.279
Standing						
Number	92	64	37	50		
LF, ln ms^2 (geometric mean)	6.23 ± 0.08 (508.7)	6.30 ± 0.09 (544.7)	6.28 ± 0.11 (532.1)	6.20 ± 0.10 (492.8)	0.885	0.769
LF (%)	82.0 ± 1.3*	86.5 ± 1.3	85.0 ± 1.7	87.3 ± 0.9	**0.016**	**0.014**
HF, ln ms^2 (geometric mean)	4.48 ± 0.10 (88.5)	4.23 ± 0.12 (68.7)	4.38 ± 0.11 (79.8)	4.15 ± 0.12 (63.6)	0.145	0.077
HF (%)	18.0 ± 1.3*	13.5 ± 1.3	15.0 ± 1.7	12.7 ± 0.9	**0.016**	**0.014**
LF/HF, ln (geometric mean)	1.75 ± 0.09† (5.75)	2.07 ± 0.10 (7.93)	1.90 ± 0.11 (6.67)	2.05 ± 0.08 (7.75)	**0.044**	**0.038**

LF (%) and HF (%) indicate percentage of LF or HF power in the range between 0.035 and 0.05 Hz (see methods for details). LF/HF indicates ratio of LF to HF power. Values are mean ± SEM; geometric means are given between parentheses. *P* values were obtained by one-way ANOVA. Adjusted *P* values were calculated after adjusting for age, BMI, and family history of hypertension, diabetes, or obesity. *P* values of less than 0.05 are shown in boldface type. ANOVA, analysis of variance; HF, high frequency; LF, low frequencyz; SEM, standard error of mean. *$P < 0.05$, compared with D/D–C/C and I allele–C/C (Bonferroni post-hoc test in adjusted model). †$P = 0.054$, compared with D/D–C/C (Bonferroni post-hoc test in adjusted model).

had a lower BMI than the C/C carriers, consistent with previous reports in Japanese and Caucasian individuals [41,59,60]. UCP3 plays a role in uncoupling oxidative phosphorylation in the skeletal muscle, heart, and adipose tissues and is thought to mediate the increase in energy expenditure [1,2]. Mice overexpressing UCP3 were shown to be hyperphagic but lean and resistant to diet-induced obesity [61]. Furthermore, UCP3 mRNA expression was positively correlated with sleeping metabolic rate [62]. Thus, with respect to these data, the increased UCP3 expression in the −55T allele carriers could be associated with increased energy expenditure, causing a body weight reduction. However, other studies found no association or opposite results in different populations [36,63]. Further studies are needed to confirm the direct effect of this polymorphism on body weight regulation.

The *UCP2* gene is adjacent to the *UCP3* gene. In the present study, modest linkage disequilibrium was found between the *UCP2* 45 bp insertion/deletion and the *UCP3* −55C/T polymorphisms. Although synergistic interaction effects between the studied polymorphisms were not observed in our populations, an additive effect was found in some HRV indices. In a standing position, participants with the D/D−T allele combined genotype had the lowest HRV sympathetic (low frequency percentage and low frequency/high frequency) and the highest HRV parasympathetic (high frequency percentage) indices among the combined genotypes, suggesting that the *UCP2* 45 bp insertion/deletion and the *UCP3* −55C/T combined genotypes could have additive effects on autonomic cardiovascular regulation. In addition, a significant association was found between the D/D−T allele genotype and a family history of hypertension, diabetes, and obesity. Follow-up studies are required to evaluate the future prevalence of these diseases in the carriers of each genotype. Recently, some studies indicated an association of variation of the *UCP2–UCP3* gene cluster with very low calorie diet-induced body fat reduction [55] and type 2 diabetes [64]. Thus, we cannot exclude the possibility that the *UCP2* 45 bp insertion/deletion or *UCP3* −55C/T polymorphisms are in linkage disequilibrium with other responsible functional polymorphisms. Therefore, haplotype or diplotype analyses for the *UCP2–UCP3* gene cluster may provide a more precise understanding of the contribution of these polymorphisms to the related (patho)physiological phenotypes.

To our knowledge, this is the first study to examine the association of the *UCP2* 45 bp insertion/deletion or *UCP3* −55C/T polymorphisms with HRV. However, there are some limitations. First, although HRV is of clinical importance in overall stability of cardiac ANS, we did not investigate the direct physiological effect of the studied *UCP* polymorphisms, such as plasma catecholamine levels. Thus, further studies combining biochemical testing with HRV analysis will help in understanding the association between *UCP2* and *UCP3* polymorphisms and ANS activity. Secondly, an interesting association was found between the *UCP2* and *UCP3* polymorphisms and a family history of hypertension, diabetes, and obesity. It is possible that these polymorphisms of *UCPs* may account for a part of the causes of these diseases. However, the present study did not use a familial-based approach, and the findings were an indirect association, which did not provide direct evidence for a heritable role of the studied *UCP* polymorphisms in the prevalence of these diseases. A further familial-based study to specifically confirm the inheritance of the *UCP2* and *UCP3* polymorphisms for the related diseases would be beneficial.

In conclusion, the present study found that the *UCP2* 45 bp insertion/deletion and the *UCP3* −55C/T polymorphisms were significantly associated with HRV as well as BMI and BP in young Japanese men. These phenotypes, according to *UCP2* and *UCP3* polymorphisms, may be potential risk factors for future pathological episodes of UCP-related diseases such as hypertension and CVD. As *UCP2* and *UCP3* expression is altered with aging [65], prospective cohort studies are necessary to investigate the long-term contributions of *UCP2* and *UCP3* polymorphisms to related (patho)physiological phenotypes.

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