30. Fischel-Ghodsian N, Prezant TR, Bu X, et al, Mitochondrial ribosomal RNA gene mutation in a patient with sporadic aminoglycoside ototoxicity. *Am J Otolaryngol.* 1993; 14:399-403.

31. Toyo-oka T, Nagayama K, Suzuki J, et al, Noninvasive assessment of cardiomyopathy development with simultaneous measurement of topical ^{1}H- and ^{31}P-magnetic resonance spectroscopy. *Circulation* 1992; 86:295-301.

32. Harris KM, Spirito P, Maron MS, et al, Ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation* 2006; 114:216-25.

33. Finnila S, Lehtonen MS, Majamaa K. Phylogenetic network for European mtDNA. *Am J Hum Genet.* 2001; 68:1475-84.

34. Herrnstadt C, Elson JL, Fahy E, et al, Red2uced-median-network analysis of complete mitochondrial DNA coding-region sequences for the major African, Asian, and European haplogroups *Am J Hum Genet*, 2002; 70:1152-71 .

35. Starikovskaya EB, Sukernik RI, Derbeneva OA, et al, Mitochondrial DNA diversity in indigenous populations of the southern belt of Siberia and its implications for the origins and evolution of Native American haplogroups. *Ann Hum Genet.* 2005; 69 (Pt 1): 67-89 .

36. Kong QP, Bandelt HJ, Sun C, et al, Updating the East Asian mtDNA phylogeny: a prerequisite for the identification of pathogenic mutations. *Human Molecular Genetics* 2006; 15: 2076-86 .

37. Tanaka M, Cabrera VM, Gonzalez AM et al, Mitochondrial genome variation in eastern Asia and the peopling of Japan *Genome Res* 2004; 14 (10A):1832-50.

38. Wang X, Lu J, Zhu Y, et al, Mitochondrial tRNAThr G15927A mutation may modulate the phenotypic manifestation of ototoxic 12S rRNA A1555G mutation in four Chinese families *Pharmacogenet Genom.* 2008; 18:1059-70.

39. Yao YG, Macauley V, Kivisild T, et al, To trust or not to trust an idiosyncratic mitochondrial data set. *Am J Hum Genet.* 2003; 72: 1341-46.

40. Broughton RE, Milam JE, Roe BA. The complete sequence of the zebrafish (Danio rerio) mitochondrial genome and evolutionary patterns in vertebrate mitochondrial DNA. *Genome Res.* 2001; 11:1958-67.

Figure legends

Fig. 1. Classic methods for the screening steps of wide variety of DCM/HCM in nuclear and mitochondrial genomes.

Fig. 2. (A) Maximum likelihood estimate of $tRNA^{Thr}$ in vertebrate phylogeny, focusing primates. Red, green and blue colored-nucleotides indicate a modifier gene of current HDCM or DCM, several neurodegenerative disease and modulator gene of LHON (Leber's hereditary optic neuropathy), respectively. (B) Maximum likelihood estimate of mtDNA in vertebrate phylogeny (Cited from, Broughton *et al., Genome Res.* 2001, Ref. 40).

Fig. 3. Less agreement of commercially available microarray, comparing between NIH SNP/SNV data and our own Database of *MYH7* gene. Note the very rare overlap among these databases and the detection rate between the two databases was 0.6% with Affymetrix, 900k-Microarray.

Fig. 3. Human mtDNA Migrations (Cited from MITOMAP: A Human Mitochondrial

Genome Database. http://www.mitomap.org, 2009).

Fig. 4. (A) Conservation of the wild-type sequence in non-human primates, suggesting the biological significance of the DNA sequence.

Table 1. Homology of mt-DNA sequence (8551-9300) to NUMT (Mitochondrial DNA-like sequences in the nucleus) of human genome.

Fig. 1

1. Case-Selection of HCM/DCM
2. Prep. of Genomic DNA from WBC from In/Out-patients, Biopsy Samples during cath. study, LVAD ope., Whole heart in autopsy or Card. transplant. (Japanese, n=79; Caucasian, n=15).
3. Two control groups from non-CM without heart failure (n=75) or normal volunteers (n=93)

↓

Clinical diagnosis of HDCM or DCM depending on patient's
1. morphology (Echo, MRI, Cath. for imaging),
2. physiology (ECG, Holter Monitoring, hemodyamics) and
3. pathology (Biopsy, Autopsy, Immunohistology or EM study *etc.* (Toyo-oka *et al., PNAS* 2004)

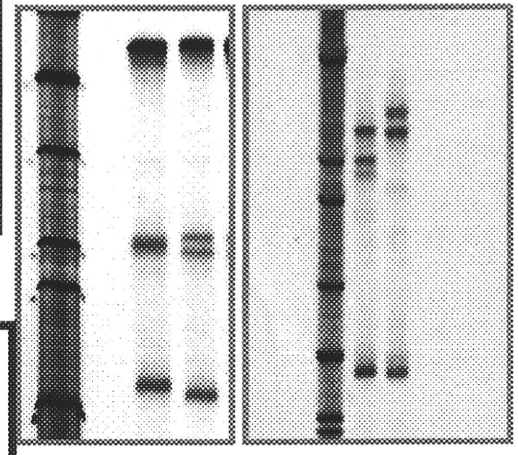
↓

Gene-screening with RFLP (Kato *et al., Lancet* 1995, Shin *et al., AJHG* 2000) or SSCP in old cases or SSPCE-FCS in new cases with 100% accuracy within 30 min for 90 cases (Hori *et al., Curr.Pharm. Biotechnol.,* 2003)

↓

1. Confirmation with direct sequencing of mt-genome or PCR products of nDNA from all candidates with HDCM/DCM
2. Heteroplasmy quantification and physiol. validation *in silico*.

PCR–SSCP



G1598A **G12192A**

PCR–RFLP

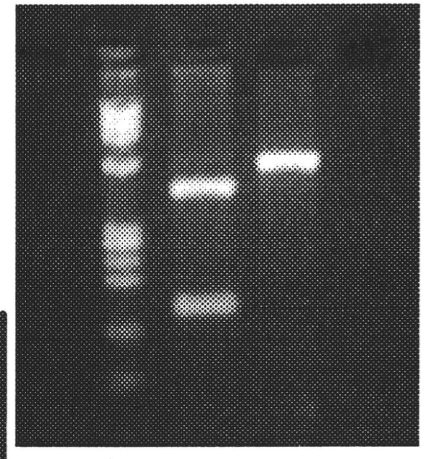


Fig. 2

A

tRNAT	species	15888	95	97	15901	7	10	11	16	23	28	32	37	40	46	53
Primates	Homo sapiens	GTCCTTG	TA	GTAT	AAACTA	ATAC	A	CCAGT	CTTGTAA	ACCGG	AGAT	GAAAA	CCT	TTTTC	CAAGGAC	A
	Gorilla gorilla	GCCCTTG	TA	GTAC	AGACCA	ATAC	A	CCAGT	CTTGTAA	ACCGG	AAAC	GAAGA	CCT	CCTTC	CAAGGGC	A
	Pan troglodytes	GCCCTTG	TA	GTAT	AAACTA	ATAC	A	CCGGT	CTTGTAA	ACCGG	AAAC	GAAAA	CTT	TCTTC	CAAGGAC	A
	Hylobates lar	GCCCTTG	TA	GTAT	AAGCCA	ATAC	A	CCGGT	CTTGTAA	GCCGG	AACT	GAAAT	CTT	CCTTC	CAAGGAC	A
	Pongo pygmaeus	GCCCCTG	TA	GTAC	AAATAA	GTAC	G	CCAGC	CTTGTAA	CCTGA	AAAT	GAAGC	CCC	CCTTC	CACGGGC	A
	Papio hamadryas	GCCCTTG	TA	GTAC	AAACTA	ATAC	A	CTGGT	CTTGTAA	ACCAG	AAAT	GGAGC	A	CCTCC	CCAGGGT	A
	Bos taurus	GTCTTTG	TA	GTAC	ATCTA	ATAT	A	CTGGT	CTTGTAA	ACCAG	AGAA	GGAGA	ACAACTAA	CCTCC	CTAAGAC	T
	Cebus albifrons	GTCCTTG	TA	GTAT	ATCCAA	TTAC	C	CCGGC	CTTGTAA	ACCGG	AAAA	GGAGG	CACGCTA	ACTCC	CCAGGAC	A
	Lemur catta	GCCCTTG	TA	GTAT	AACTTA	ATAC	C	CTGGT	CTTGTAA	ACCAG	ACAT	GGAGA	ACCCCCT	CCTCC	CAAGGAC	A
	Macaca mulatta	GCCCTCG	TA	GTAT	AAATTA	GTAC	A	CTGGC	CTTGTAA	ACCAG	AAAT	GAACA	C	TCTTC	CTAGGGC	A
	Tarsius bancanus	GTCCTCG	TA	GTAT	AACCA	TTAC	C	TTGGT	CTTGTAA	ACCAA	AAAT	GAAGG	AACCCAA	CCTCC	CTAGGAC	C
Dermoptera	Cynocephalus variegatus	GTCCCTG	TA	GTAT	AATAA	TTAC	T	CTAGT	CTTGTAA	ACCAG	AAAT	GGAGG	GAGCAC	CCTCC	CCAGGAC	A
Oryctero-podidae	Orycteropus afer	GTCCTTG	TA	GTAT	AAACTA	TTAC	C	ATGGT	CTTGTAA	ACCAT	AAAT	GGATC	TAAC	CCTCC	CCAGGAC	A
Cetartio-dactyla	Balaenoptera acutorostrata	GTCTTTG	TA	GTAT	AACTAA	TTAC	C	CCGGT	CTTGTAA	ACCGG	AAAA	GGAGA	GCGAACCACA	CCTCC	CTAAGAC	T

B

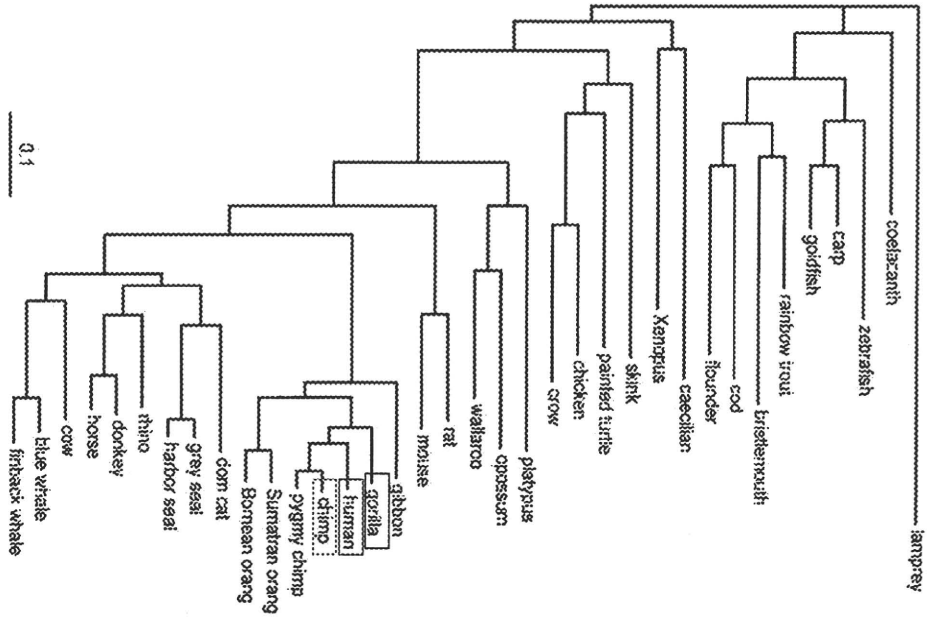
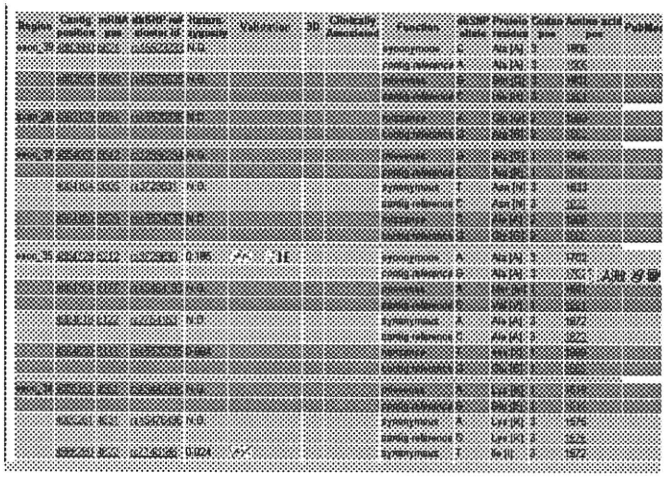
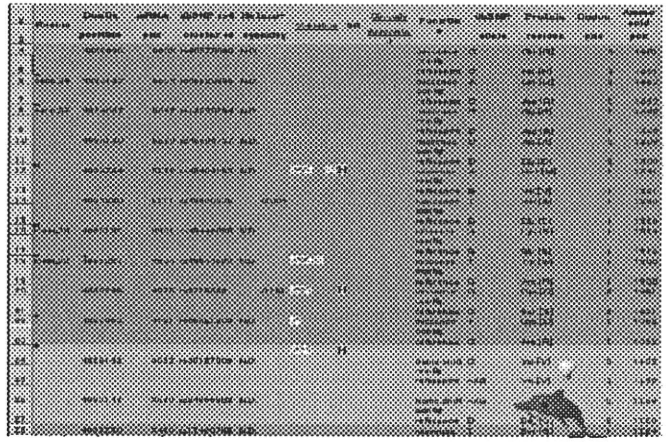


Fig. 3

A



B



Non-syn. SNP=36

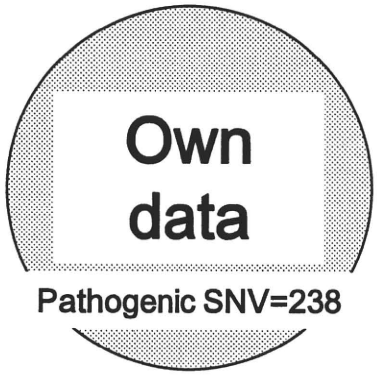
C

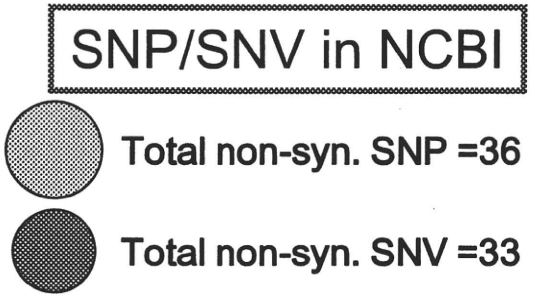
Total SNP=78

	A	B	C	D	E	F	G	H	I	J
176	FHD0116	MYH7	exon 11	c. 7543GDC	A25P	confirmed	Dowello DA, et al. Am J Hum Genet 1997 61:A329 [Abstract]	codon change, coding, missense	substitution	neutral charge substitution
177	FHD1025	MYH7	exon 11	c. 7525 GDA	V22M	confirmed	Hevndrup O / Christiansen M, et al. Cardiovasc Res 2000 57:347-57	codon change, coding, missense	substitution	neutral charge substitution
178	FHD1026	MYH7	exon 11	c. 7550 AG	E23G	confirmed	Sawyer NA / Yu B, et al.(Sydney, Australia) July 2000 Direct submission.	codon change, coding, missense	substitution	net charge substitution -1 to 0
179	FHD0116	MYH7	exon 11	c. 7543GDC	A25P	confirmed	Dowello DA, et al. Am J Hum Genet 1997 61:A329 [Abstract]	codon change, coding, missense	substitution	neutral charge substitution
180	FHD1025	MYH7	exon 11	c. 7525 GDA	V22M	confirmed	Hevndrup O / Christiansen M, et al. Cardiovasc Res 2000 57:347-57	codon change, coding, missense	substitution	neutral charge substitution
181	FHD1026	MYH7	exon 11	c. 7550 AG	E23G	confirmed	Sawyer NA / Yu B, et al.(Sydney, Australia) July 2000 Direct submission.	codon change, coding, missense	substitution	net charge substitution -1 to 0
182	FHD1028	MYH7	exon 12	c. 8266 AG	K35E	confirmed	Sawyer NA / Yu B, et al.(Sydney, Australia) July 2000 Direct submission.	codon change, coding, missense	substitution	net charge substitution +1 to -1
183	FHD1029	MYH7	exon 12	c. 8266 AG	K35E	confirmed	Sawyer NA / Yu B, et al.(Sydney, Australia) July 2000 Direct submission.	codon change, coding, missense	substitution	net charge substitution +1 to -1
184	FHD0116	MYH7	exon 13	c. [8808CDG;88 10GDT]	L39OV	confirmed	Andersen PS, et al. HGM99 Brisbane Australia 1999[Abstract]	codon change, coding, missense	substitution	neutral charge substitution
185	FHD0117	MYH7	exon 13	c. 8848GDA	R40Q	confirmed	Georgakopoulos D / Kass DA, et al. Nat Med 1999 5:327-30; Marian AJ / Roberts R, et al. Eur Heart J 1995 16:369-76; Fananapazir L / Epstein ND. Circulation 1995 92:685-92; Geisterfer-Lowrance A / Seidman CE, et al. Cell 1990 62:999-1006	codon change, coding, missense, nonconservative	substitution	net charge substitution +1 to Q, located in t affect actin-myosin interaction;mouse mode contraction, increased end-systolic chamber
186	FHD0118	MYH7	exon 13	c. 8847CDT	R40W	confirmed	Rosen BM / Brink PA, et al. Br Heart J 1995 74:40-6; Al-Mahdawi S / Oakley C, et al. Br Heart J 1994 72:105-11; Deusee E / Guicheney P, et al. J Clin Invest 1993 92:2907-12; Modmen JD / Corfield VA, et al. Hum Mol Genet 1992 1:31-7	codon change, coding, missense, nonconservative	substitution	net charge substitution +1 to Q, located in t after globular head conformation; may reduce effecting actin-myosin interaction
187	FHD0119	MYH7	exon 13	c. 8849CDT	R40L	confirmed	Ravment I / Epstein ND, et al. Proc Natl Acad Sci USA 1995 92:3864-8; Al-Mahdawi S / Oakley C, et al. Br Heart J 1994 72:105-11; Deusee E / Guicheney P, et al. J Clin Invest 1993 92:907-12	codon change, coding, missense, nonconservative	substitution	net charge substitution +1 to Q, located in t after globular head conformation; may reduce effecting actin-myosin interaction
188	FHD0120	MYH7	exon 13	c. 8788GDT	K26N	confirmed	Kuang SQ / Chen Z, et al. J Mol Cell Cardiol 1996 28:1879-83	codon change, coding, missense, nonconservative	substitution	net charge substitution +1 to 0
189	FHD0194	MYH7	exon 13	c. 8856GDA	V40M	confirmed	Greber-Platzer S / Wimmer M, et al. J Mol Cell Cardiol 2001 33:161-6	codon change, coding, missense	substitution	neutral charge substitution located in the a
190	FHD0195	MYH7	exon 13	c. [8823insG; 8850delG]	[del395 *404h s395RA CGSLP PSLI	confirmed	Dute G/Metticli PL, et al. Heart 1996; 76: 451-2	frame, 2 frameshifts resulting in 10 codon changes	10 aa substitutions (395*404)	

Pathogenic SNV=238 in Own Database

D





Very rare overlap,
Detection rate 0.6% with Affymetrix,
900k-Microarray.

Fig. 4

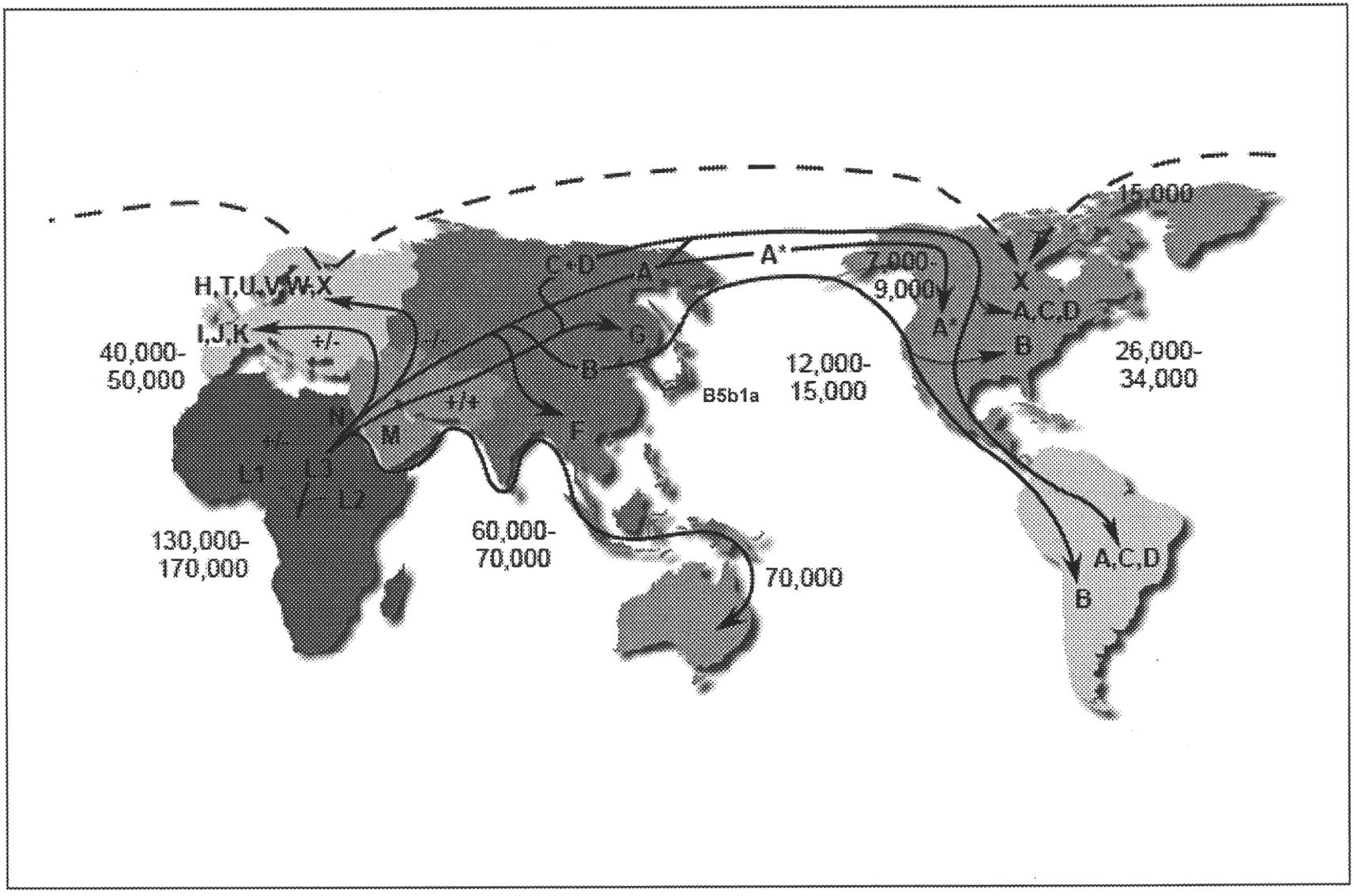

15,000
C+D
A
A*
7,000-
9,000
X
A,C,D
H,T,U,V,W,X
I,J,K
+/-
+/-
G
A*
B
40,000-
50,000
B
12,000-
15,000
B5b1a
26,000-
34,000
+/+
N
M
F
+/-
L1
L3
L2
130,000-
170,000
60,000-
70,000
70,000
A,C,D
B

Table. 1

Sequences producing significant alignments			
Accession	Description	E value	Max ident
NC_001807.4	Homo sapiens mitochondrion, complete genome	0	99%
NT_004350.19	Homo sapiens chromosome 1 genomic contig, GRCh37 reference primary assembly	0	98%
NT_034772.6	Homo sapiens chromosome 5 genomic contig, GRCh37 reference primary assembly	0	88%
NW_001838563.2	Homo sapiens chromosome 1 genomic contig, alternate assembly (based on HuRef), whole genome shotgun sequence	0	98%
NT_022184.15	Homo sapiens chromosome 2 genomic contig, GRCh37 reference primary assembly	4.00E-91	96%
NT_167187.1	Homo sapiens chromosome 8 genomic contig, GRCh37 reference primary assembly	2.00E-55	85%
NW_001839126.2	Homo sapiens chromosome 8 genomic contig, alternate assembly (based on HuRef), whole genome shotgun sequence	2.00E-55	85%
NW_923907.1	Homo sapiens chromosome 8 genomic contig, alternate assembly (based on Celera), whole genome shotgun sequence	2.00E-55	85%
NT_032977.9	Homo sapiens chromosome 1 genomic contig, GRCh37 reference primary assembly	2.00E-29	100%
NW_001838577.2	Homo sapiens chromosome 1 genomic contig, alternate assembly (based on HuRef), whole genome shotgun sequence	2.00E-29	100%
NW_921351.1	Homo sapiens chromosome 1 genomic contig, alternate assembly (based on Celera), whole genome shotgun sequence	2.00E-29	100%
NT_007299.13	Homo sapiens chromosome 6 genomic contig, GRCh37 reference primary assembly	2.00E-24	86%
NW_001838987.1	Homo sapiens chromosome 6 genomic contig, alternate assembly (based on HuRef), whole genome shotgun sequence	2.00E-24	86%
NW_923184.1	Homo sapiens chromosome 6 genomic contig, alternate assembly (based on Celera), whole genome shotgun sequence	2.00E-24	86%

Adaptive servo ventilation improves cardiac dysfunction and prognosis in heart failure patients with Cheyne-Stokes respiration

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A running head: ASV for Heart failure with Cheyne-Stokes

Key words: heart failure, Cheyne-Stokes respiration, adaptive servo ventilation, cardiac function, prognosis

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ABSTRACT

Backgrounds: Cheyne-Stokes respiration (CSR) is often associated in patients with heart failure (HF). Although adaptive servo ventilation (ASV) is effective for CSR, it remains still unclear whether ASV improves cardiac function and prognosis of patients with HF and CSR. **Methods:** Sixty patients with HF and CSR (mean left ventricular ejection fraction 38.7%, mean apnea hypopnea index 36.8 times/hr, mean central apnea index 19.1 times/hr) were enrolled in this study. Patients were divided into two groups: 23 patients treated with ASV (ASV group) and 37 patients treated without ASV (Non-ASV group). Measurement of plasma B-type natriuretic peptide (BNP) levels and echocardiography were performed before, 3 and 6 months after treatments in each group. Patients were followed up for cardiac events (cardiac death and re-hospitalization) after discharge. **Results:** In ASV group, NYHA functional class, BNP levels, cardiac systolic and diastolic function were significantly improved with ASV treatment for 6 months. In contrast, any of these parameters did not change in Non-ASV group. Importantly, Kaplan-Meier analysis clearly demonstrated that event free rate was significantly higher in ASV group than in Non-ASV group. **Conclusions:** Adaptive servo ventilation improves cardiac function and prognosis in heart failure patients with Cheyne-Stokes respiration.

INTRODUCTION

Heart failure (HF) is a prevalent syndrome with poor prognosis, especially the major cause of death in the elderly. Identification of factors that contribute to increased mortality might lead to the development of a new strategy to improve survival of HF.[1-3] It has been reported that about 50% of HF patients have sleep apnea syndrome (SAS), which consists of obstructive sleep apnea (OSA) and Cheyne-Stokes respiration (CSR) with central sleep apnea (CSA). OSA is thought to be caused by upper airway obstruction during sleep, while the instability of respiratory control is the major cause of CSR-CSA.[4] SAS, either OSA or CSR-CSA, results in multiple pathological consequences such as an imbalance in myocardial oxygen delivery/ consumption, activation of sympathetic nervous system and other neurohurmoral factors, and increased right and left ventricular afterload.[4-6] Adaptive servo ventilation (ASV) is a ventilator support system specifically designed to normalize ventilation in patients with CSA.[4] ASV has an automatic airway tracing feedback function, and several advantages of ASV has been reported over continuous positive airway pressure (CPAP), Bi-level PAP, and O_2.[7-8] ASV can regulate the airway ventilation volume upon demand based on the variable tidal volume throughout the period of CSR. In addition, ASV automatically provides positive pressure ventilation during apnea, when necessary.

Treating SAS may improve cardiac function in patients with HF. It has been reported that CPAP suppresses the abnormal breathing pattern, attenuates sympathetic activity,[9] and improves cardiac function defined as left ventricular ejection fraction (LVEF) in HF patients with either OSA or CSR-CSA.[10] However, it still remains controversial whether CPAP can be an alternative therapeutic option in HF patients with SAS. A large-scale randomized clinical trial, the Canadian Continuous Positive

Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP), has showed that CPAP does not improve a long-term transplant-free survival of HF patients with CSR-CSA.[4, 11-12] In CANPAP subanalysis, improvement of CSR is important for cardiac function and prognosis in HF patients.[12] It is well recognized that compliance with CPAP is one of problems in treating SAS, particularly in HF patients. Therefore, other treatment options with better compliance such as ASV that can suppress SAS more effectively are needed to resolve whether SAS should be treated in HF patients. Although there are a few reports about effects of ASV on cardiac function,[4, 13-16] it has not been rigorously examined whether ASV can improve the long-term prognosis in HF patients with CSR-CSA.

Therefore, the aim of this study was to examine whether ASV improves cardiac function and prognosis in HF patients with CSR-CSA during sleep.

METHODS

Subjects and study protocol

In the present study, 176 patients with HF were recruited (Figure 1). After receiving standard pharmacotherapy for HF, polysomnography was performed. Written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of the Fukushima Medical University. The inclusion criteria were (1) the presence of symptomatic HF, which was defined as an New York Heart Association (NYHA) class II or greater, (2) standard pharmacotherapy (including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β blockers and diuretics) based on a guideline, (3) stable clinical status, which was defined as receiving optimal medical therapy and without worsening of HF at least 3

month in prior to study enrollment, and (4) diagnosed as having moderate-severe CSR-CSA, which was defined as apnea-hypopnea index (AHI) $\geq$ 15. The exclusion criteria were (1) age < 20 or > 80 years, (2) severe valvular heart disease, (3) resynchronization therapy within 6 months in prior to study enrollment, (4) the presence of severe chronic pulmonary disease, (5) on dialysis, and (6) history of stroke with neurological deficit.[4]

We screened polysomnography for consecutive 176 HF patients (NYHA II or greater) between April 2007 and December 2009. Polysomnography revealed the presence of CSR-CSA in 70 patients. Out of 70 patients, 10 patients were excluded, and 60 patients, who met the inclusion criteria, were finally enrolled in this study (Figure 1). While 37 patients once agreed to use ASV, 23 patients did not. However, after ASV try, 13 of 37 patients declined continuous therapy with ASV because of the following reasons: economic reason (n=7), mask intolerance (n=6), subjective intolerance to positive airway pressure (n=3), and no specific reason (n=2). Therefore, 24 of 37 patients finally hoped to use ASV continuously. After 1 month follow-up, one patient stopped ASV use due to mask problem and intolerance to positive airway pressure. Consequently, the patients were divided into 2 groups: 23 patients treated with ASV more than a half year (ASV group) and 37 patients without ASV (Non-ASV group) as demonstrated in Figure 1.

Plasma B-type natriuretic peptide (BNP) levels and echocardiographic parameters were determined before, 3 and 6 months after treatments in each group. Patients were followed up for cardiac events including cardiac death and re-hospitalization due to worsening heart failure after discharge.

Polysomnography

All subjects underwent overnight polysomnography with the use of standard techniques and scoring criteria for sleep stages and arousals from sleep.[17-18] Overnight complete polysomnography was performed using a computerized system (Alice5, Philips Respironics, Murrysville, PA, USA) that consisted of monitoring of the electro-encephalogram, electro-oculogram, submental electromyogram, electrocardiogram, thoracoabdominal motion, oronasal airflow by an airflow pressure transducer, and arterial oxyhemoglobin saturation (SpO_2) by pulse oximetry.[4, 17-19] Sleep disordered breathing specialists analyzed the data. Apnea was defined as an absence of inspiration without ribcage and abdominal motion for more than 10 s. Hypopnea was defined as a $\geq$ 30% reduction in monitored airflow accompanied by a decrease in SaO_2 of $\geq$ 4%.[4, 17-19] Arousal responses were defined according to the recommendations of the American Sleep Disorders Association. The AHI was defined as the number of apnea and hypopnea episodes per hour of sleep. A central apnea was defined as the absence of oronasal airflow for > 10 s associated with an absent inspiratory effort. CSR event was considered when polysomnography revealed a waxing and waning pattern of ventilation with an arousal at peak ventilation, followed by a period of apnea with absence of respiratory effort.[4, 17-19] Finally, CSR-CSA was defined as apnea-hypopnea index was over 15 times/h, and a ratio of CSR-CSA to total apnea events was over 50%.[4] The major polysomnographic parameters investigated were AHI, central apnea index (CAI), obstructive apnea index (OAI), minimal pulse oxygen saturation ($MinSpO_2$), 3% oxidative desaturation index (3%ODI), mean pulse oxygen saturation (Mean SpO_2), arousal index, total sleep time (TST), stage I + II/TST (%), stage III + IV/TST (%), and rapid eye movement (REM) sleep/TST (%), %time <

SpO_2 90%/TST (CT90), and %time < SpO_2 95%/TST (CT95) as previously reported.[4, 17-19]

Echocardiography

Echocadiography was performed using the standard techniques. Two dimensional echocardiographic images were acquired from the parasternal long and short axis, apical long axis, and apical four chamber views by an echocardiographer who was blind to the patients' clinical data. Echocardiographic parameters investigated were left ventricular mass index (LVMI), left atrial volume index (LAVI), left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), left ventricular ejection fraction (LVEF), estimated right ventricular systolic pressure (RVPS), and E/E'. The severity of mitral regurgitation (MR) was graded using a 5-point scoring system as follows: 0 = none, 1 = trivial, 2 = mild, 3 = moderate and 4 = severe. The LVEDVI, LVESVI, LVEF and LAVI were calculated using a modification of Simpson's method. E/E' was calculated by transmitral Doppler flow and tissue Doppler imaging. All recordings were performed on ultrasound systems (Acuson Sequoia, Siemens, Erlangen, Germany).

Measurement of plasma B-type natriuretic peptide (BNP) Level

The plasma BNP level was measured using a specific immunoradiometric assay (Shionoria BNP kit, Shionogi, Osaka, Japan).

Adaptive servo ventilation

We used two types of ASV (HEART PAP or BiPAP autoSV, Philips Repironics, Murrysville, PA, USA). Then, patients underwent a titration of the device during overnight attended by polysomnography. At the time of titration, we set expiratory positive airway pressure (EPAP) to disappear OSA, and next set pressure support (PS) and inspiratory positive airway pressure (IPAP) to disappear CSR.[4]

Statistical Analysis

Data are presented as mean ± SD, unless otherwise stated for continuous variables. Unpaired t test was used for normally distributed data, and Mann-Whitney U test was used for non-normally distributed data. A value of $P < 0.05$ was considered significant for all comparisons. Event free rate was analyzed by the Kaplan-Meier method, and comparisons were done by the log-rank test. All analyses were performed using a stastical software package (StatView version 5.0, SAS Institute Inc, Abacus Concepts, Berkeley, CA, USA).

RESULTS

Clinical charactaristics of study subjects

Clinical characteristics of ASV and Non-ASV groups are shown in Table 1. There were no differences in baseline clinical data between ASV and Non-ASV groups.

Baseline data of echocardiography and spirogram are shown in Table 2. Mean LVEF was 38.7%. There were no significant differences in all parameters.

Results of polysomnographic recordings at the time of diagnosis and ASV initiation are shown in Table 3. AHI and 3% ODI were higher, and lowest SpO_2 and

mean SpO_2 were lower in ASV group than in Non-ASV group. These data suggest that ASV group tended to have more severe CSR-CSA than Non-ASV group.

Effects of adaptive servo ventilation on polysomnographic data

We set ASV by attend manual titration as shown in Table 4. We set EPAP to disappear OSA, and next set PS and IPAP to disappear CSR. Finally, mean EPAP was 6.0 mmHg, mean minimum IPAP was 6.6 mmHg, and mean max IPAP was 12.5 mmHg in the present study. All patients were successfully titrated on ASV.

Table 5 shows polysomonograpgic data at baseline and on ASV in ASV group. ASV improved polysomnographic findings such as AHI, CAI, arousal index, 3%ODI, Lowest SPO_2, Mean SPO_2, CT90, CT95, and sleep efficacy. A half year later, compliance and efficacy data were downloaded from the device, and the data are summarized in Table 4. The recorded average AHI was 2.3 ± 0.5 times/h, device %usage of days was mean 79.7% of days, mean usage time was 377.6 min/day, and 4h > usage was 53.6%.

Effects of adaptive servo ventilation on cardiac function

Mean NYHA functional class improved from 2.5 to 1.6 in ASV group as shown in Table 6. In ASV group, there was a significant reduction of plasma BNP concentration after 6 months. In addition, day time $PaCO_2$ level was significantly increased after 6 months of ASV treatment. In contrast, NYHA functional class, BNP and $PaCO_2$ did not change in Non-ASV group.

Time courses of cardiac function determined by echocardiography are shown in Table 7. In ASV group, LVEDVI, LVESVI, LVEF, LVMI, LAVI, RVPs, E/e', and

MR score were significantly improved with ASV treatment for 6 months. In contrast, any of these parameters did not change in Non-ASV group.

Comparison of event free rate between ASV and Non-ASV groups

During follow-up period (mean 355 days, range 185-1040), there were 17 cardiac events including 5 cardiac deaths and 12 re-hospitalizations from worsening heart failure. In ASV group (n=23), one patient died because of ventricular fibrillation and one patient re-hospitalized for worsening heart failure. In Non-ASV group (n=37), 4 patients died because of ventricular fibrillation (n = 1) and progression of heart failure (n = 3), and 11 patients re-hospitalized. As shown in Figure 2, Kaplan-Meier analysis clearly demonstrated that event free rate was significantly higher in ASV group than in Non-ASV group ($P<0.01$).

DISCUSSION

In this study, ASV treatment for 6 months during sleep improved not only CSR-CSA but also functional status of heart failure and cardiac function. Echocardiography clearly showed that ASV improved cardiac systolic and diastolic function accompanied by the reduction of left ventricular volume and functional MR. Furthermore, event free rate in ASV group was significantly higher than in Non-ASV group. This is the first report, to our knowledge, demonstrating that ASV improved event free survival rate in HF patients with CSR-CSA.

Effects of heart failure treatment on Cheyne-Stokes respiration

Effective therapies for HF including optimal pharmacotherapy and cardiac resynchronization therapy (CRT) improve the severity of CSR-CSA,[20-22] but effects of such therapies for HF are not sufficient enough for CSR-CSA.[20-25] In the present study, 12 patients at least 12 months after CRT implantation are included, and CSR-CSA and depressed cardiac function still remained in spite of standard pharmacotherapy and CRT in those patients.

Effects of treatment for Cheyne-Stokes respiration on heart failure

Whether treatment of CSR-CSA contributes to improvement in cardiac function and prognosis in HF patients is still uncertain.[20-22] Several studies have reported improvement in cardiac function by positive airway pressure ventilation treatment.[4, 7, 26-28] Recently, a randomized controlled prospective study in treating HF and CSR has shown that ASV improves AHI and compliance (average usage time) more effectively than CPAP.[13] They have also reported that LVEF improves (average +9%) by ASV, but not by CPAP. In the present study, we clearly showed that ASV improved cardiac systolic and diastolic function accompanied by the reduction of left ventricular volume. However, it remains still unknown whether ASV improves prognosis of patients with HF and CSR-CSA. In the present study, we demonstrated that ASV improved event free rate in patients with HF and CSR-CSA, although ASV group included more severe CSR-CSA than Non-ASV group.

Possible mechanisms for improvement in heart failure by ASV

Several possible mechanisms of ASV to improve HF with CSR have been considered as follows: (1) reduce the upper airway obstruction, (2) increase