

# Heritability and linkage study on heart rates in a Mongolian population

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Abbreviations: *ADRB1*, adrenergic receptor gene; AMI, acute myocardial infarction; AR, androgen receptor; *CAV3*, caveolin 3 gene; CVD, cardiovascular disease; *F12*, coagulation factor XII gene; *ET2*, endothelin 2 gene; *LIPG*, Endothelial lipase precursor gene; EL, endothelial lipase; GENDISCAN, gene discovery for complex traits in isolated large families of Asians of Northeast; HDL-C, high density lipoprotein cholesterol; MCP1, monocyte chemoattractant protein 1; *ZC3H12A*, zinc finger CCCH type containing 12A gene; *NSD1*, nuclear receptor SET domain containing gene 1; IBD, identity by descent; IHD, ischemic heart disease; SOLAR, sequential oligogenic linkage analysis routines; SNP, single nucleotide polymorphism; *SLC14A2*, solute carrier family 14 gene; TG, triglyceride; *E2F3*, E2F transcription factor 1 gene; UT-A protein, urea transporter protein; VC, variance component

## Abstract

Elevated heart rate has been proposed as an in-

dependent risk factor for cardiovascular diseases, but their interrelationships are not well understood. In this study, we performed a genome-wide linkage scan in 1,026 individuals (mean age 30.6 years, 54.5% women) from 73 extended families of Mongolia and determined quantitative trait loci that influence heart rate. The DNA samples were genotyped using deCODE 1,039 micro-satellite markers for 3 cM density genome-wide linkage scan. Correlation analysis was carried out to evaluate the correlation of the covariates and the heart rate. T-tests of the heart rate were also performed on sex, smoking and alcohol intake. Consequently, this model was used in a nonparametric genome-wide linkage analysis using variance component model to create a multipoint logarithm of odds (LOD) score and a corresponding *P* value. In the adjusted model, the heritability of heart rate was estimated as 0.32 (*P* < .0001) and a maximum multipoint LOD score of 2.03 was observed in 77 cM region at chromosome 18. The second largest LOD score of 1.52 was seen on chromosome 5 at 216 cM. Genes located on the specified locations in chromosomes 5 and 18 may be involved in the regulation of heart rate.

**Keywords:** cardiovascular diseases; chromosome mapping; genomics; heart rate; Mongolia

## Introduction

Epidemiological and clinical studies suggest that elevated heart rate is a potential risk factor for a variety of cardiovascular diseases (CVD) including atherosclerosis, coronary artery disease (CAD), myocardial infarction, arterial hypertension and heart failure (Greenland *et al.*, 1999; Colhoun *et al.*, 2001; King *et al.*, 2006; Palatini *et al.*, 2006; Brasel *et al.*, 2007; Fox *et al.*, 2007; Rogowski *et al.*, 2007). The elevated heart rate is closely associated with age, high blood pressure, body mass index (BMI), smoking, alcohol consumption, high cholesterol level, and physical inactivity. But, even after adjusting for other potential risk factors, elevated heart rate remains significantly associated with CVD, mortality and all cause mortality in patients with CVD as well as general population (Kannel WB *et al.*, 1987; Gillman *et al.*, 1993; Palatini 1999; Kristal-Boneh *et al.*, 2000; Fujiura *et al.*, 2001; Kovar *et al.*, 2004; Diaz *et al.*, 2005; Fox

*et al.*, 2007; Reil and Bohm 2007; Theobald *et al.*, 2007). The mechanism for elevated heart rate and its association with such diseases and death is still not well understood. A number of twin and family studies have reported that genetic factors influence the regulation of heart rate (Singh *et al.*, 1999; Woodman *et al.*, 2002; Wilk *et al.*, 2002; Martin *et al.*, 2004; Neumann *et al.*, 2005; Laramie *et al.*, 2006; Larson *et al.*, 2007; Newton-Cheh *et al.*, 2007; O'Donnell *et al.*, 2007). Voss *et al.* (1996) reported that there is a genetic component in heart rate generation and heart rate variability in monozygotic and dizygotic twin pairs. Singh *et al.*, (2002) identified significant genetic regions contributing to heart rate variability on chromosome 15 at 62 cM and chromosome 2 at 153 cM. In the recent meta-analysis of genome-wide scans for study networks that enrolled Caucasians and African-Americans, Laramie *et al.* (2006) concluded in the replication between various ethnic groups as well as the study networks with low heterogeneity on chromosome 5p13-14. Wilk *et al.* (2002) also identified that 195.06 cM region of chromosome 4 is seemingly related to the variability in resting heart rate.

Most published studies on genetic influences on the variation of heart rate focused on Caucasian and not on Asian populations. The genetic background and environmental factors to which a subject group is exposed differ in every human population. In this study, we assessed genetic components involved in heart rate variation using data from gene discovery for complex traits in isolated large families of Asians of Northeast (GENDISCAN) study. Large extended families enable the full utilization of family design for linkage study. GENDISCAN study is committed to incorporating most of methodological issues of complex diseases using genetically homogeneous population and emphasizing the quantitative phenotypes.

## Materials and Methods

### Subjects

One thousand and twenty six Mongolian individuals (54.5% women) from 73 extended families from Dornod, Mongolia were genotyped. Informed consents to participate in the study were obtained from all subjects. The protocol for GENDISCAN study was approved by the institutional review board (IRB) of Seoul National University of Korea (approval number, H-0307-105-002).

### Heart rate and covariates

Four consecutive measurements of the heart rate and blood pressure were made on both arms of each participant while seated, employing a standard electronic sphygmomanometer. When the four blood pressure measurements differed by more than 10 mmHg, a fifth measurement was made and the lowest four were used in the analyses. The larger means of each set of measurements were accepted as heart rate and the blood pressure respectively. Measurements in children from age 10 to 16 were made using appropriate cuffs and a mercury sphygmomanometer. Data on potentially confounding factors for heart rate such as age, sex, smoking, and alcohol consumption were collected through interviews performed by trained interviewers. The standing height in centimeter (cm) and weight in kilograms (kg) were measured, and BMI was calculated in  $\text{kg}/\text{m}^2$ .

### Genotyping

For those who agreed to be genotyped, genomic DNA was extracted from peripheral venous blood leukocytes using standard procedure and genotyped using deCODE 1,039 microsatellite marker platform. Whole genome analyses have been performed. For 1,039 deCODE marker sets, optimized multiplex PCR reactions were set up on Zymark ALH 400, run on MJR Tetrad and pooled on Gilson Cyberlab C200 robots. The reaction volume was 5  $\mu\text{l}$ , and for each PCR 20 ng of genomic DNA was amplified in the presence of 2 pmol of each primer, 0.25 U AmpliTaq Gold, 0.2 mM dNTPs and 2.5 mM  $\text{MgCl}_2$  (buffer was supplied by the manufacturer, Applied Biosystems). Cycling conditions were as follows: 95°C for 10 min, followed by 37 cycles of 94°C for 15 s, annealing for 30 s at 55°C, and 1 min extension at 72°C. The PCR products were supplemented with the internal size standard GS500-LIZ, and the pools were separated and detected on 3730 Sequencers. Alleles were automatically called using DAC, an allele-calling program developed at deCODE genetics Inc. and the program deCODE GT was used to fractionate called genotypes, according to quality, and to edit when necessary.

### Statistical analysis

**Correlation analysis:** We carried out a correlation analysis to evaluate the correlation of covariates (age, sex, smoking, alcohol intake, brachial systolic pressure, brachial diastolic pressure, brachial mean arterial pressure and body mass index) and heart rate, and Pearson correlation coefficients were identified. T-tests of heart rate were also performed

on the three categories, which are sex, smoking and alcohol intake, by using SAS statistical software version 9.1.

#### **Pedigree and genotype data cleaning, single- and multi-point identity by descent (IBD) calculation:**

For the family relationship, nonpaternity was examined using PEDCHECK. Relationships other than paternity were checked using average identity by descent (IBD)-based method by PREST. After correcting pedigree error and mendelian errors, non-mendelian errors were examined and corrected using SimWalk. After pedigree and genotype errors were corrected, IBD matrices between every relationship pair were calculated. IBD matrix for single marker was calculated by SOLAR, and multipoint IBD (MIBD) matrices were computed on every 1 cM distance using Markov chain Monte Carlo method by LOKI. We used Haldane's mapping function to convert map distances into recombination fractions.

**Heritability estimation:** Genetic components of selected phenotypes were estimated in terms of heritability. Narrow sense heritability, defined as the proportion of total phenotypic variation due to additive genetic effects, was calculated. Age-sex adjusted phenotype (adjusted for age, sex, age-square, product of age and sex, product of age-square and sex) was estimated by SOLAR for quantitative traits.

**Multipoint variance component-based linkage analysis for heart rate:** To reduce the type I error from deviated distribution, original values were normalized using Z-transformation. The genetic variance of heart rate was decomposed into specific additive genetic effects from specific markers (Quantitative trait loci, QTL) and non-QTL given by:

$$\Omega_{ij} = \pi \sigma_{qtl}^2 + 2\Phi_{ij} \sigma_{n-qtl}^2 + I e^2$$

Where  $\Omega$  is the covariance matrix of the entire family,  $\pi$  is a matrix of the proportions of the specific QTL that the relative pairs share as IBD,  $\Phi$  is a kinship matrix,  $I$  is an identity matrix,  $\sigma_{qtl}^2$  is specific QTL effects of the genetic markers,  $\sigma_{n-qtl}^2$  is residual genetic effect, and  $e^2$  is random environmental effects and errors. The likelihood that QTL effects can be estimated were compared with the likelihood of null hypothesis that specific QTL effect equals zero. The logarithm of odds (LOD) score between likelihood of null and alternative hypothesis was used to test the significance of linkage results. The multipoint linkage analyses were performed using SOLAR. In the genome-wide scans, age, sex, age<sup>2</sup> and the interactions between them

retained in the models as covariates at  $P < 0.10$ . Because variance composition method is sensitive to outliers, multivariate residual kurtosis in each analysis retained less than 0.8 thereby avoiding type 1 error.

## **Results**

Demographic and pedigree characteristics of the data set and the covariates are presented in Table 1. The data set of examined individuals included a large number of relative pair types as we have recruited extended families. The data set included information on 2,546 pairs of first-degree relatives (1,812 parent-offspring pairs and 734 full-sib pairs), and 2,485 pairs of their second-degree relatives (395 half-sibling pairs, 1,202 grandparent-grandchild pairs). The other 888 and 598 pairs were avuncular and first-cousins, respectively. Current alcohol use and smoking was reported by 13.4% and 19.1%, of the subjects, respectively. Mean age of the subjects was 30.6 yrs. Mean resting heart rate was 78.1 and the mean number of family members was 15.7. The mean BMI was 23.4 and the mean brachial systolic, diastolic, and arterial

**Table 1.** Demographic and pedigree characteristics of the dataset.

Characteristic	Value
No. of families	73
Mean $\pm$ SD no. of family members (range)	15.7 $\pm$ 12.4
No. of genotyped subjects	1026
Mean $\pm$ SD age (in years)	30.6 $\pm$ 15.4
Percentage female (%)	54.5
Height (cm)	155.8 $\pm$ 11.1
Weight (kg)	58.0 $\pm$ 15.6
Body mass index (kg/m <sup>2</sup> )	23.4 $\pm$ 4.5
Brachial systolic pressure (mmHg)	114.6 $\pm$ 16.3
Brachial diastolic pressure (mmHg)	67.3 $\pm$ 9.8
Brachial Mean arterial pressure (mmHg)	83.1 $\pm$ 11.7
Heart rate (bpm)	78.1 $\pm$ 10.9
Current alcohol use (%)	131 (13.4)
Smoking (%)	190 (19.1)
No. of study pairs of :	
Parent-offspring	1,812
Full-sib pairs	734
Sisters	198
Brothers	167
Brother and sister	369
Half-sib pairs	395
Grandparent-grandchild pairs	1,202
Avuncular pairs	888
First-cousin pairs	598

blood pressure was 114.6, 67.3, and 83.1, respectively. Table 2 shows the relationships between baseline characteristics and heart rate. Age, brachial diastolic pressure, and BMI were significantly associated with mean heart rate. The adjusted heritability model includes age, gender, BMI, smoking and alcohol consumption. In the adjusted model, the heritability of heart rate was estimated to be 0.32 ( $P < .0001$ ). In Table 3 are presented LOD scores greater than 1.0, nearest markers, chromosomal locations and candidate genes. In the adjusted model a maximum LOD score of 2.03 was seen on chromosome 18 at 77 cM. The second largest LOD score of 1.52 was seen on chromosome 5 at 216 cM. Figure 1 shows the chromosomal regions linked to heart rate

genome-wide linkage analysis. As shown in Figure 2, there is suggestive evidence of linkage (LOD score = 2.03) of a quantitative trait locus (QTL) for heart rate on chromosome 18 at 77 cM.

## Discussion

It has long been known that heart rate is under the control of the parasympathetic and sympathetic nervous system, and that heightened sympathetic tone increases the heart rate (Bonaa and Arnesen, 1992; Palatini and Julius, 1997; Rahn *et al.*, 1999; Fujiura *et al.*, 2001). In more recent studies, they pointed out that genetic components may play an essential role in the regulation of heart rate variability. The Framingham heart study (Singh *et al.*, 1999) also demonstrated that genetic factors are involved in heart rate variability. The degree of heritability of heart rate was 0.32 in GENDISCAN study. This value is somewhat higher than the figure (0.21) reported for Framingham Heart Study participants (Singh *et al.*, 1999), but is lower than the figure (0.41) reported for participants of Netherlands Twin Register (Kupper *et al.*, 2004). All the three studies provide evidence for a strong genetic component in heart rate variability.

We showed a peak with a maximum LOD of 2.03 on chromosome 18 at 77 cM. As described by Duchesne *et al.* (2001), *SLC14A2* (solute carrier family 14 urea transporter) gene which lies near this loci, encodes UT-A protein expressed in the heart. The expression of this protein in failing left ventricle is 1.4-4.3 fold to that in normal nonfailing ventricle. Further, *LIPG* (endothelial lipase precursor) gene also lies on chromosome 18 at 77cM. This gene encodes the protein that process substantial phospholipase activity and plays an important role in lipid metabolism. More recently, Shimizu *et al.* (2007) reported that the significant association between 584C/T SNP of *LIPG* gene and an acute

**Table 2.** Relationships between baseline characteristic data and heart rate.

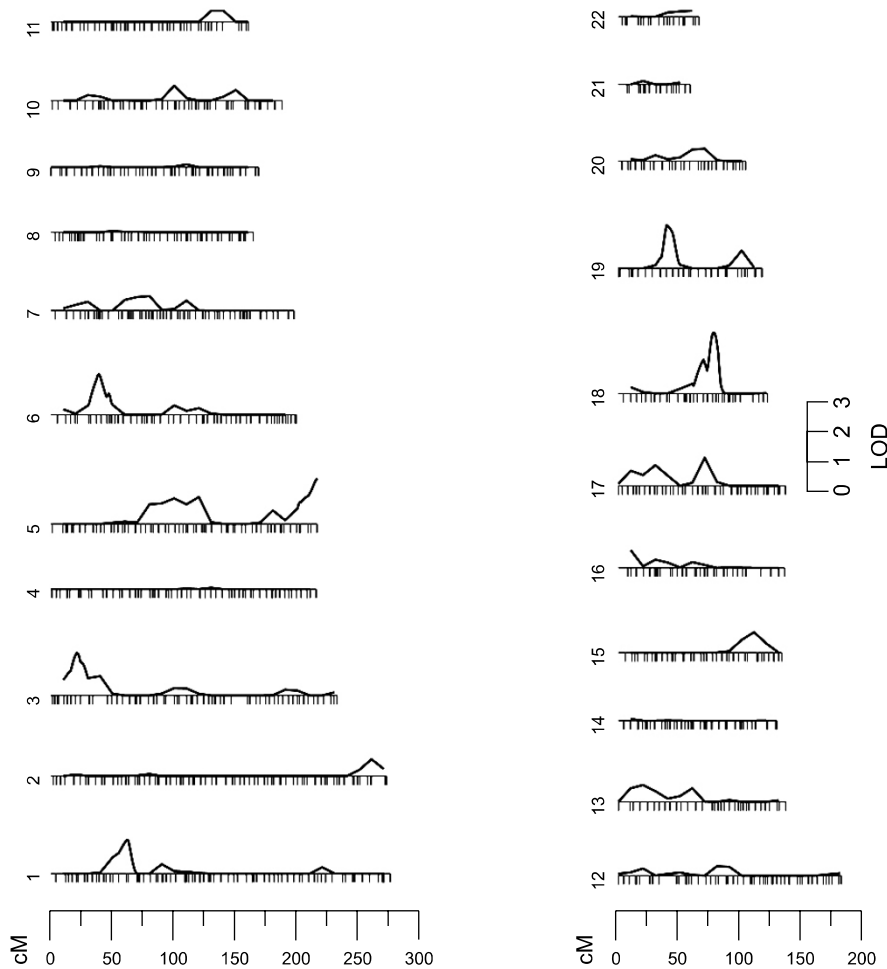
	Heart rate
<b>Pearson correlation coefficients</b>	
Age	-0.21 (< .0001)
Brachial systolic pressure	-0.01 (0.72)
Brachial diastolic pressure	0.11 (0.0002)
Brachial Mean Arterial pressure	0.06 (0.07)
Body mass index (kg/m <sup>2</sup> )	-0.21 (< .0001)
<b>Mean values (SD)</b>	
Gender (t-test) <sup>a</sup>	0.60
Women	78.3 ± 10.4
Men	77.0 ± 11.5
Smoking (t-test) <sup>b</sup>	0.35
Yes	77.5 ± 11.4
No	78.3 ± 10.7
Alcohol (t-test) <sup>c</sup>	0.53
Yes	77.5 ± 10.8
No	78.1 ± 10.9

<sup>a</sup> $P$  values reflect test of subgroup differences (women versus men). <sup>b</sup> $P$  value of smoking yes, no; <sup>c</sup> $P$  value of alcohol yes, no

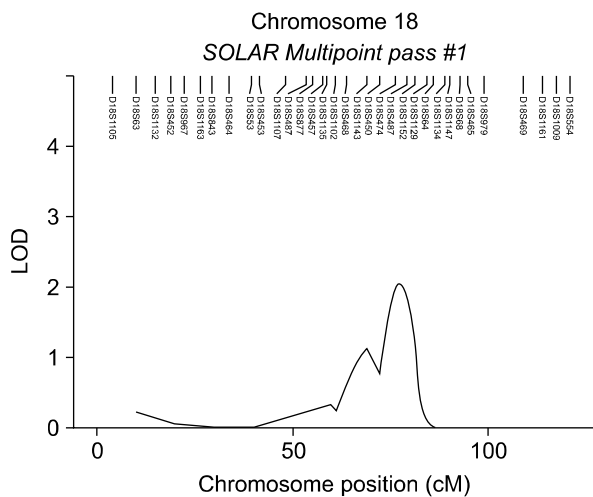
**Table 3.** LOD scores, chromosomal locations, and nearest marker data for all LOD scores > 1.00<sup>a</sup>.

Trait	Marker at or Near Peak	Chromosome Location	deCODE (cM)	Maximum LOD gene	Candidate Score
Heart rate	D1S186	1	62	1.13	<i>ET2</i> <i>ZC3H12A</i>
	D3S1515	3	21	1.32	<i>CAV3</i>
	D5S408	5	216	1.52	<i>NSD1</i> <i>F12</i>
	D6S1567	6	39	1.35	<i>E2F3</i>
	D18S474	18	77	2.03	<i>LIPG</i> <i>SLC14A2</i>

<sup>a</sup>Includes adjustment for age, gender, BMI, smoking and alcohol.



**Figure 1.** Genome-wide linkage analysis of chromosomal regions linked to heart rate.



**Figure 2.** Evidence of linkage (LOD score = 2.03) of a quantitative trait locus (QTL) for heart rate on chromosomes 18 at 77 cM.

myocardial infarction (AMI) independent of HDL-C levels in a Japanese population. It is also of interest that chromosome 5 yielded the second largest linkage peak which corresponds to its 216 cM region. An analysis of the database indicated that the chromosomal region 216 cM on chromosome 5 contains *NSD1* (nuclear receptor SET domain containing gene1) gene. The protein encoded by *NSD1* gene enhances transactivation of androgen receptor (AR). It has been reported that the intra-genic mutation of this gene is associated with the high frequency of congenital heart defects or heart conduction (Cecconi *et al.*, 2005). *F12* (coagulation factor XII) gene also located at 216 cM on chromosome 5 encodes coagulation factor XII, which circulates in blood as a zymogen. Roldan *et al.*, (2005) reported that the C46T polymorphism of *F12* is associated with a reduction of plasma FXII levels and a development of myocardial infarction (MI), particularly in hypercholesterolemic patients. Santamaria *et al.* (2004) also reported that the homozygosity for the C46T polymorphism of the

F12 gene is significantly associated with high risk of coronary artery disease (CAD) in the Spanish population. Moreover, the *ZC3H12A* (zinc finger CCCH type containing 12A) gene was located at 62cM on chromosome 1, which is an MCP1 (monocyte chemotactic protein-1) induced protein. Recent study of Zhou *et al.*, (2006) reported that MCP-1 causes cell death of cardiomyocytes and plays an important role in the development of ischemic heart disease (IHD). Also, the *ET2* (endothelin 2) gene at 62 cM on chromosome 1 was founded. Sharma *et al.* (1999) reported that polymorphism in the *ET2* gene influences the hypertension when blood pressure is assessed as a quantitative trait. Moreover, *E2F3* gene at 39 cM on chromosome 6 encodes a transcription factor of the E2F family. This family protein has an important role of controlling tumor suppressor proteins and cell cycle. The region at 21 cM on chromosome 3 includes *CAV 3* gene, which encodes caveolin-3 muscle-specific protein. This finding is interesting in the background of evidence that cav-3 null mice show perivascular fibrosis, cellular infiltration in cardiac tissue and cardiac myocyte hypertrophy, which exhibits inter- and intrafamilial variations ranging from benign to malignant forms with high risk of cardiac failure and sudden cardiac death (Cribbs *et al.*, 2001; Woodman *et al.*, 2002; Chen *et al.*, 2003; Ha *et al.*, 2005).

In conclusion, we identified susceptible loci for heart rate variability in an Asian population. This study strongly indicates that heart rate is controlled by genes mapped to several loci. We believe characterization of genes that affects heart rate variability can lead to unraveling of the pathogenetic mechanisms underlying heart rate variability and its association with CVD and to rational therapeutic interventions.

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