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Genome-Wide Scan to Identify Quantitative Trait Loci for Baseline Resting Heart Rate and Its Response to Endurance Exercise Training: The HERITAGE Family Study

Abstract

Evidence of a genetic component for resting heart rate (RHR) has been found. Quantitative trait loci (QTLs) for baseline RHR have been reported, but not for RHR training response. It is of interest to identify QTLs that may harbor genes influencing RHR variation at baseline and in response to regular exercise training. Here, a multipoint variance components linkage scan using 654 markers was performed to search for QTLs that influence RHR adjusted for several covariates at baseline and in response to 20 weeks of endurance training (post-training minus baseline) in 99 White and 127 Black families in the HERITAGE Family Study. Potentially interesting linkages were revealed on 4 q and 11 p for baseline RHR, and on 1 q and 21 q for RHR training response in Whites. The QTLs on 2 q, 6 q, 7 q, 12 q, 14 q, and 15 q for baseline RHR, and on 3 p, 20 p and 21 q for RHR training response were found in Blacks. Promising linkages (lod scores ≥ 1.75, $p \leq 0.0023$) involved 11 p for baseline RHR in Whites and 3 p for RHR training response in Blacks, which did not replicate across races. Interestingly in this study, the linkage evidence on 11 p at the *SUR* locus was somewhat enhanced (lod score went up from 1.7 to 2.0) in a prehypertensive (BP $\geq$ 135/80 mm Hg) subset of 40 White families suggesting a pleiotropic gene for BP and RHR with interactions. In conclusion, among QTLs on 1 q, 2 p, 3 p, 4 q, and 11 p that replicated across subsamples and studies, 11 p is most promising for dense mapping and association studies in HERITAGE and other cohorts.

Key words
Variance components multipoint linkage analysis · Whites · Blacks

Introduction

Elevated resting heart rate (RHR) is a predictor of cardiovascular and noncardiovascular mortality [7]. RHR is thought to result from the balance of sympathoexcitatory and parasympathoinhibitory activities, and the contribution from several cardiovascular risk factors such as physical inactivity, cigarette smoking, abnormal lipid profile, and elevated blood pressure (BP) [20,22]. Recent studies consistently support a genetic component for RHR [15,16], with heritability estimates of about 30% for RHR at baseline [1] and about 30% for its response to 20 weeks of endurance exercise-training (post-training minus baseline) [13] in the HERITAGE Family Study. There is also evidence of a major gene effect for baseline RHR in White families, and a major effect for

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Bibliography
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Table **1** Data description for unadjusted RHR (beats/min) in Whites and Blacks

Variables	*Number*	*Means*	*SD*	*Number*	*Means*	*SD*
Whites		**fathers**			**mothers**	
Age (years)	99	53.5	5.3	95	52.0	5.1
BMI (kg/m²)	98	28.4	4.4	94	27.6	5.0
Baseline RHR	97	63.9	7.7	94	66.7	8.8
Response RHR	92	–3.6	5.7	90	–2.5	6.2
		sons			**daughters**	
Age (years)	163	25.2	6.0	171	25.4	6.3
BMI (kg/m²)	161	25.6	4.9	168	23.7	4.5
Baseline RHR	159	60.8	8.6	170	67.2	8.6
Response RHR	140	–3.6	6.3	156	–2.5	6.7
Blacks		**fathers**			**mothers**	
Age (years)	29	50.0	7.2	60	46.6	6.6
BMI (kg/m²)	29	27.5	5.2	59	29.4	5.2
Baseline RHR	29	63.6	9.1	57	69.4	7.5
Response RHR	22	–2.7	6.4	46	–2.4	6.4
		sons			**daughters**	
Age (years)	88	27.0	7.2	149	27.6	7.5
BMI (kg/m²)	86	27.4	5.8	147	27.9	7.0
Baseline RHR	84	62.7	8.4	146	69.1	8.6
Response RHR	63	–3.4	6.5	117	–2.2	8.6

RHR training response in a prehypertensive (BP ≥ 135/80 mm Hg) subset of White families in the HERITAGE Family Study [2].

Two previous linkage scans identified quantitative trait loci (QTLs) on chromosomes 15 q and 2 q for heart rate variability in the Framingham Heart Study (FHS) [17], and on 4 q and 10 q for RHR among hypertensives in the Hypertension Genetic Epidemiology Network (HyperGEN) study [21], but QTLs for RHR training response were not yet assessed. Here we performed genome-wide linkage scans to identify QTLs that influence baseline RHR and its training response in sedentary White and Black families who participated in the HERITAGE Family Study.

Materials and Methods

The HERITAGE Family Study design, protocol, population, inclusion and exclusion criteria have been described elsewhere [3]. Subjects were required to be in good health so as to complete a 20-week exercise-training program. Subjects were sedentary at baseline, having engaged in no regular vigorous exercise in the previous 6 months. They were ≤ 65 years for parents and ≥ 17 years for offspring. BP was ≤ 159/99 mm Hg, and BMI was ≤ 40 kg/m². None of the subjects took antihypertensive or antidyslipidemia medications. Several subjects whose BMI was slightly higher than 40 kg/m² were approved for participation by supervising physicians. The sample sizes within 8 sex-by-generation-by-race groups are given in Table **1**. A total of 528 individuals (262 men and 266 women) from 99 White families and 326 individuals (117 men and 209 women) from 127 Black families have complete data. Here, the prehypertensive subsample (40 White families) is defined as at least one family member whose baseline resting BP is in the high end of the normal BP range (the upper 95% percentile of the HERITAGE cohort: BP ≥ 135/80 mm Hg) [2,5]. The Institutional Review Boards at all the five participating centers approved the study protocol. Written informed consents were obtained from all participants.

Multiple RHR and resting BP (RBP) measurements were made on 2 separate days, both at baseline and after 20 weeks of participation in a standardized exercise-training program as described elsewhere [18]. RHR and RBP measurements were obtained before 11 : 00 a.m. with participants in a 12-hour fasted state and having consumed no tobacco products for at least 2-hours prior to assessment. Measurements were performed in a quiet room after participants were rested for at least 5 min in a reclining chair with legs elevated and the chair back reclined at about 45°. ECG was used to record RHR. RBP was determined using a properly fitted cuff connected to a Colin STBP-780 automated unit (San Antonio, Texas, USA). At least 4 RHR and RBP readings were taken following the initial 5-min rest with 2-min intervals between readings. The first measurement was discarded though recorded on the paper form. The data used here represent the average of up to 6 measurements. RHR change in response to training was computed as post-training minus baseline. BMI was computed as weight in kilograms over height squared in meters (kg/m²).

Baseline RHR was adjusted for the effects of age and BMI within each of the 8 sex-by-generation-by-race groups using a stepwise multiple regression procedure. It was regressed on a polynomial in age (age, age², and age³) and BMI in a stepwise manner retain-

ing only those terms that were significant at the 5% level. Thus, the residual score from this regression is independent of age, BMI, sex, generation, and race effects. RHR change in response to training was adjusted for the effects of a polynomial in age, BMI, and baseline RHR within each of the 8 groups. Each of the final adjusted phenotypes was finally standardized within sex-by-generation groups separately by race (mean = 0, SD = 1).

PCR conditions and genotyping methods were described elsewhere [4]. Mendelian inheritance incompatibilities were checked. Markers with incompatibilities were re-genotyped (< 10%). Microsatellite markers were mainly selected from the Marshfield panel (v. 8a). Map locations in Location Database (LDB) composite units for markers were derived from the Location Database of Southampton, UK (http://cedar.genetics.soton.ac.uk/public_html). The LDB units were obtained by integrating different types of data (genetic linkage maps, radiation hybrid maps, physical maps, cytogenetic data, and mouse homology) and constructing a single summarized map. The data were obtained from internet, published sources and Wessex Human Genetics Institute. In this study, LDB units were used for performing the genome-wide linkage scan, and physical distance in Mb obtained from NCBI physical map build 34.3 was used for presenting the linkage results.

Multipoint variance components linkage analysis was performed using the computer program SEGPATH [10,11]. Under this model, a phenotype is influenced by additive effects of a trait locus *(g)*, a residual familial background modeled as a pseudopolygenic component *(G_R)* and a residual nonfamilial component *(r)*. The effects of the trait locus and the residual pseudopolygenic component on the phenotype are quantified by the heritabilities, h^2_g and h^2_r, respectively. Allele-sharing probabilities at each marker location for each sibpair were estimated using the multipoint approach in the computer program MAPMAKER/SIBS [8], and were used as input in the SEGPATH model. Other parameters in this model include spouse *(u)* and additional sibling *(b)* resemblance, and the phenotype mean and variance in the offspring. The linkage hypothesis was tested by restricting $h^2_g = 0$. A likelihood ratio test contrasting the null ($h^2_g = 0$) versus the alternative (h^2_g estimated) hypothesis is asymptotically distributed as a 50 : 50 mixture of a χ^2 with 1 degree of freedom and a point mass at 0 [14]. The lod score was computed as $\chi^2/(2 \times \log_e 10)$.

Results

In this study, the coefficient of variation and intraclass correlation for repeated RHR measurements were 8% and 0.73, respectively [19]. Means and standard deviations (SDs) of unadjusted baseline RHR and its training response were presented in Table **1**. Mean RHR was higher ($p < 0.05$) in mothers than in fathers, and was higher in daughters than in sons. No generation differences in mean RHR were noted except that mean RHR was higher in fathers than in sons in Whites. There were no sex or generation differences in mean RHR changes in response to 20 weeks of endurance training.

For baseline RHR, BMI accounted for 7.5%, 7.8%, and 15.2% of RHR variation in White sons, Black mothers, and Black sons, respectively, but was not a significant term in any other group. Age was not a significant predictor of baseline RHR. For RHR training response in Whites, baseline RHR, BMI, and age terms accounted for about 30% of the variation in fathers and sons, and about 20% in mothers and daughters. For the training response in Blacks, the same covariates accounted for about 30% of RHR variation in fathers, mothers and sons, and 13.5% in daughters.

A total of 654 microsatellite and single nucleotide polymorphism markers covering all autosomes were typed. The average inter-marker spacing was 2.6 Mb. The mean heterozygosities were 0.72 (± 0.15) in Whites and 0.76 (± 0.16) in Blacks. The linkage scan results for baseline RHR and its training response on all 22 autosomes were depicted in Fig. **1A** for Whites and Fig. **1B** for Blacks. Potentially interesting linkage results ($p \leq 0.01$, lod score ≥ 1.18) from both races were detailed in Table **2**. Of the promising linkage signals (lod score ≥ 1.75, $p \leq 0.0023$) [21], the linkage on 11 p15.1 at the sulfonylurea receptor *(SUR)* gene (17.392 Mb) was with the best lod score in Whites for baseline RHR. This linkage signal slightly enhanced (lod scores from 1.7 to 2.0) in the prehypertensive subsample of 154 sib-pairs from 40 White families. No other promising linkages were detected in Whites in both the prehypertensive and remaining subsamples for both phenotypes. We did not perform subsample linkage scans in Blacks because the sample size was small. Other interesting linkages on 1 q, 2 q, 3 p, and 4 q will be discussed.

Discussion

In the current study, significant linkages (lod score ≥ 3.63, $p \leq 0.000\,022$) were not detectable, partially because of the fact that RHR belongs to a complex trait under influences of multiple genes as well as unmeasured genetic and environmental interactions. Previous family studies have evidenced that the genetic component underlying RHR variation is significant but moderate in magnitude [1,2,13]. Here, although some replications across studies and phenotypes were found, we also found that some of our findings did not replicate QTLs on chromosome 15 from the FHS [17] and 10 from the HyperGEN subjects [21]. One explanation would be that the scan in FHS employed a different phenotype, heart rate variability [18], versus RHR in this study. Also, the scan in HyperGEN was performed in hypertensive subjects [21] in contrast to sedentary nonhypertensives in the present study.

The linkage signal on 11 p15.1 at the *SUR* gene (17 Mb; OMIM 600 509) was enhanced (lod scores went up from 1.70 to 1.98) in the prehypertensive subsample of Whites (Table **2**). The subset of families with prehypertension may be biologically more homogeneous than the complete sample, or the QTL may have a pleiotropic effect on RHR and BP. SUR is one of two subunits that comprise membrane-bound ATP-sensitive potassium ion channels mediating glucose-stimulated insulin secretion. The *SUR* encoding gene is a plausible candidate for primary pancreatic β-cell defect and thus for hyperglycemia [8]. Relationship between HR and insulin sensitivity and insulin secretion has been reported in nondiabetic subjects previously [6]. In the present study, 11 p15.1 is the best genomic region for baseline RHR in Whites

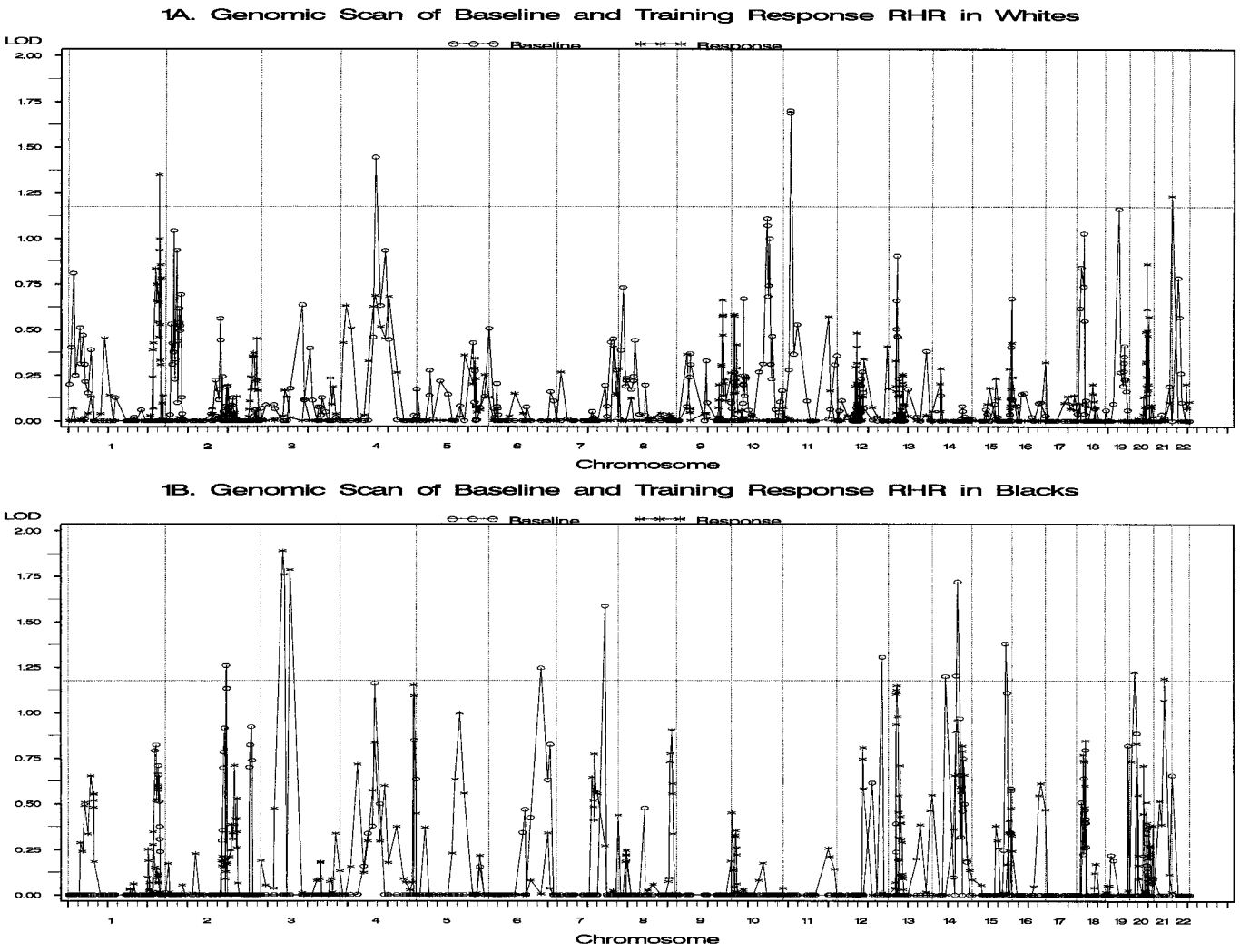

Fig. **1 A** and **B** An overview of autosomal linkage scan results for baseline RHR and its training response in Whites (**A**) and Blacks (**B**). Lod score of the horizontal reference line is 1.18 (p = 0.01) for potentially interesting linkage.

(whole sample as well as prehypertensive subsample). Further studies on this region should be pursued.

Two interesting replications should be highlighted. First, the QTL on 4 q35.1 at marker D4S408 (186 Mb, lod score 1.1; Fig. **1**) for RHR training response in Blacks replicated HyperGEN findings for baseline RHR in Whites (lod score 2.14), Blacks (lod score 1.14), and a combined analysis of two racial groups (lod score 3.18) [21]. RHR training response and baseline RHR are two different phenotypes. Since RHR training response was induced by an environmental exposure, the QTL may be part of the ability to change HR in response to regular exercise. Within 2 Mb of D4S408, there are two speculated candidates involving in cardiac morphogenesis; they are the *SLC25A4* (solute carrier family 25, member 4) gene (OMIM 103,220) and the *ALP* (actinin-associated LIM protein) gene (187 Mb; OMIM 605,889). The *SLC25A4* gene expresses ADP/ATP translocator or adenine nucleotide translocator (ANT) in human heart and skeletal muscle that is the most abundant mitochondrial protein. The *ALP* gene expresses ACTN2 (actinin α-2) – associated LIM protein whose skeletal, cardiac, and smooth muscle isoforms join to anchor the myofibrillar actin filaments. The *HAND2* (heart and neural crest derivatives expressed 2) gene (186 Mb, 4 q33, OMIM 602 407) also involves in cardiac morphogenesis, and has been mentioned as a possible candidate gene previously [21]; however, this gene is about 10 Mb away from the current linkage peak at D4S408.

Second, the QTL on 1 q42.12 (D1S439, 223 Mb, lod score 0.82; Fig. **1**) for baseline RHR in Blacks was close to QTL at 1 q42.2 (D1S251, 229 Mb, lod score 1.35) for RHR training response in Whites. The nearby *AGT* (angiotensin I) gene (1 q42.2, 227 Mb; OMIM 106 150), known to influence human BP, could be a candidate for this QTL.

Other linkage signals detected for baseline RHR included 4 q22.1 at D4S1534 (87 Mb, lod score 1.44) in Whites, corresponding to a linkage in Blacks at the same marker location (lod score 1.16), and 2 q23.3 at D2S2275 (152 Mb or 161 cM, lod score 1.26) in Blacks, corresponding to a linkage (153 cM, lod score 1.81) reported in FHS [18]. We also identified promising linkages on 3 p (D3S1447, 55 Mb, lod score 1.89; D3S1766, 59 Mb, lod score 1.76; D3S2406, 73 Mb, lod score 1.78) in Blacks. There are no known candidates for RHR in the immediate vicinity of these QTLs.

In conclusion, genomic regions that may harbor genes influencing RHR at baseline and in response to endurance training were

Table **2** Summary of potentially interesting multipoint linkages ($p \leq 0.01$, LOD score ≥ 1.18)

Chromosome	*Marker*	*Distance (Mb)*	*LOD in Whites*		*LOD in Blacks*	
			Baseline	*Response*	*Baseline*	*Response*
1q42.2	D1S251	228.749	0.00	1.35	0.58	0.12
2q23.3	D2S2275	152.024	0.19	0.00	1.26	0.13
3p14.2	D3S1447	54.851	0.00	0.03	0.00	1.89
3p21.2	D3S1766	58.939	0.00	0.17	0.00	1.76
3p14.1	D3S2406	73.179	0.18	0.02	0.00	1.78
4q22.1	D4S1534	86.767	1.44	0.69	1.16	0.83
4q35.1	D4S408*	185.847	0.00	0.00	0.85	1.09
6q23.1	D6S1040	130.966	0.00	0.00	1.24	0.01
7q31.33	D7S3061	122.844	0.19	0.00	1.59	0.27
11p15.1	SURBSIEI#	17.392	1.70 (1.98)#	0.00 (0.23)#	0.00	0.00
11p15.1	SURPSTI#	17.394	1.69 (1.74)#	0.00 (0.24)#	0.00	0.00
12q24.22	D12S2070	114.495	0.00	0.00	1.31	0.01
14q13.1	D14S599	32.644	0.00	0.00	1.20	0.00
14q23.1	D14S592	59.387	0.00	0.00	1.20	0.90
14q23.2	D14S63	62.641	0.00	0.00	1.72	0.96
15q25.1	D15S152	83.613	0.00	0.00	1.38	0.00
20p11.23	D20S604	12.579	0.00	0.00	0.00	1.22
21q21.1	D21S2052	27.740	0.02	0.00	0.00	1.19
21q22.3	D21S1446	46.894	0.00	1.23	0.66	0.02

* Linkage results at the marker D4S408, though with lod scores < 1.18, are also presented in this table for reference of replication with other studies (see Discussion).
# SURBSIEI is a polymorphism for the sulfonylurea receptor gene exon 22, and SURPSTI is a polymorphism from the sulfonylurea receptor gene intron 24. The lod scores in parentheses are results in the prehypertensive subgroup of White families

localized on 11 p, along with 1 q, 2 q, 3 p, and 4 q, in sedentary White and Black families. Further fine mapping and association studies on 11 p are justified because of the best linkage signal detected in a large sample of White families with linkage evidence enhancement in the prehypertensive subsample of Whites.

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References

[1] An P, Rice T, Gagnon J, Borecki IB, Pérusse L, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Familial aggregation of resting blood pressure and heart rate in a sedentary population. The HERITAGE Family Study. Am J Hypertens 1999; 12: 264 – 270
[2] An P, Rice T, Pérusse L, Borecki IB, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Complex segregation analysis of resting blood pressure and heart rate measured before and after a 20-week endurance exercise training program: The HERITAGE Family Study. Am J Hypertens 2000; 13: 488 – 497
[3] Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. The HERITAGE Family Study: Aims, design and measurement protocol. Med Sci Sports Exerc 1995; 27: 721 – 729
[4] Chagnon YC, Borecki IB, Pérusse L, Roy S, Lacaille M, Chagnon M, Ho-Kim MA, Rice T, Province MA, Rao DC, Bouchard C. Genome-wide search for genes related to the fat-free body mass in the Quebec family study. Metabolism 2000; 49: 203 – 207
[5] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003; 289: 2560 – 2571
[6] Festa A, D'Agostino R Jr, Hales CN, Mykkanen L, Haffner SM. Heart rate in relation to insulin sensitivity and insulin secretion in nondiabetic subjects. Diabetes Care 2000; 23: 624 – 628
[7] Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, Stamler J. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. Am J Epidemiol 1999; 149: 853 – 862
[8] Hani EH, Clement K, Velho G, Vionnet N, Hager J, Philippi A, Dina C, Inoue H, Permutt MA, Basdevant A, North M, Demenais F, Guy-Grand B, Froguel P. Genetic studies of the sulfonylurea receptor gene locus in NIDDM and in morbid obesity among French Caucasians. Diabetes 1997; 46: 688 – 694
[9] Kruglyak L, Lander ES. Complete multipoint sib-pair analysis of qualitative and quantitative traits. Am J Hum Genet 1995; 57: 439 – 454
[10] Province MA, Rao DC. A general purpose model and a computer program for combined segregation and path analysis (SEGPATH): Automatically creating computer programs from symbolic language model specifications. Genet Epidemiol 1995; 12: 203 – 221
[11] Province MA, Rice TK, Borecki IB, Gu C, Kraja A, Rao DC. Multivariate and multilocus variance components method, based on structural re-

lationships to assess quantitative trait linkage via SEGPATH. Genet Epidemiol 2003; 24: 128 – 138
[12] Rao DC, Province MA. The future of path analysis, segregation analysis, and combined models for genetic dissection of complex traits. Hum Hered 2000; 50: 34 – 42
[13] Rice T, An P, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Heritability of HR and BP response to exercise training in the HERITAGE Family Study. Med Sci Sports Exerc 2002; 34: 972 – 979
[14] Self GA, Liang KY. Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. J Am Stat Assoc 1987; 82: 605 – 610
[15] Sinnreich R, Friedlander Y, Luria MH, Sapoznikov D, Kark JD. Inheritance of heart rate variability: the kibbutzim family study. Hum Genet 1999; 105: 654 – 661
[16] Singh JP, Larson MG, O'Donnell CJ, Tsuji H, Evans JC, Levy D. Heritability of heart rate variability: the Framingham Heart Study. Circulation 1999; 99: 2251 – 2254
[17] Singh JP, Larson MG, O'Donnell CJ, Tsuji H, Corey D, Levy D. Genome scan linkage results for heart rate variability (The Framingham Heart Study). Am J Cardiol 2002; 90: 1290 – 1293
[18] Skinner JS, Wilmore JH, Krasnoff JB, Jaskolski A, Jaskolska A, Gagnon J, Province MA, Leon AS, Rao DC, Wilmore JH, Bouchard C. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. Med Sci Sports Exerc 2000; 32: 157 – 161
[19] Stanforth PR, Gagnon J, Rice T, Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH. Reproducibility of resting blood pressure and heart rate measurements: The HERITAGE Family Study. Ann Epidemiol 2000; 10: 271 – 277
[20] Williams PT, Haskell WL, Vranizan KM, Blair SN, Krauss RM, Superko HR, Albers JJ, Frey-Hewitt B, Wood PD. Associations of resting heart rate with concentrations of lipoprotein subfractions in sedentary men. Circulation 1985; 71: 441 – 449
[21] Wilk JB, Myers RH, Zhang Y, Lewis CE, Atwood L, Hopkins PN, Ellison RC. Evidence for a gene influencing heart rate on chromosome 4 among hypertensives. Hum Genet 2002; 111: 207 – 213
[22] Zhang J, Kesteloot H. Anthropometric, lifestyle and metabolic determinants of resting heart rate: A population study. Eur Heart J 1999; 20: 103 – 110