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CREB1 Is a Strong Genetic Predictor of the Variation in Exercise Heart Rate Response to Regular Exercise

The HERITAGE Family Study

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Background—A genome-wide linkage scan identified a quantitative trait locus for exercise training–induced changes in submaximal exercise (50 W) heart rate (ΔHR50) on chromosome 2q33.3-q34 in the HERITAGE Family Study (n=472).

Methods and Results—To fine-map the region, 1450 tag SNPs were genotyped between 205 and 215 Mb on chromosome 2. The strongest evidence of association with ΔHR50 was observed with 2 single-nucleotide polymorphisms (SNPs) located in the 5′ region of the cAMP-responsive element-binding protein 1 (*CREB1*) gene (rs2253206: $P=1.6\times10^{-5}$ and rs2360969: $P=4.3\times10^{-5}$). The associations remained significant ($P=0.01$ and $P=0.023$, respectively) after accounting for multiple testing. Regression modeling of the 39 most significant SNPs in the single-SNP analysis identified 9 SNPs that collectively explained 20% of the ΔHR50 variance. *CREB1* SNP rs2253206 had the strongest effect (5.45% of variance), followed by SNPs in the *FASTKD2* (3.1%), *MAP2* (2.6%), *SPAG16* (2.1%), *ERBB4* (3 SNPs≈1.4% each), *IKZF2* (1.4%), and *PARD3B* (1.0%) loci. In conditional linkage analysis, 6 SNPs from the final regression model (*CREB1, FASTKD2, MAP2, ERBB4, IKZF2*, and *PARD3B*) accounted for the original linkage signal: The log of the odds score dropped from 2.10 to 0.41 after adjusting for all 6 SNPs. Functional studies revealed that the common allele of rs2253206 exhibits significantly ($P<0.05$) lower promoter activity than the minor allele.

Conclusions—Our data suggest that functional DNA sequence variation in the *CREB1* locus is strongly associated with ΔHR50 and explains a considerable proportion of the quantitative trait locus variance. However, at least 5 additional SNPs seem to be required to fully account for the original linkage signal. **(*Circ Cardiovasc Genet*. 2010;3:294-299.)**

Key Words: exercise ■ genetics ■ heart rate ■ fine mapping ■ quantitative trait locus

Regular physical activity is universally accepted as a central component of a heart-healthy lifestyle. The risks of cardiovascular morbidity and mortality are considerably lower in physically active individuals compared with their sedentary counterparts. Cardioprotective effects of regular exercise are usually associated with improvements in traditional cardiovascular disease risk factors: lower blood pressure and plasma low-density lipoprotein cholesterol levels and increased plasma high-density lipoprotein cholesterol levels. However, regular physical activity also induces beneficial changes in cardiac function. For example, a physically active individual can perform the same amount of physical work with less strain on the heart (indexed as lower heart rate and blood pressure during a given work output) than a person who is sedentary.

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Clinical Perspective on p 299

In the HERITAGE Family Study, a highly standardized and fully supervised (100% compliance) 20-week endurance training program induced an average decrease of 11.3 bpm in heart rate measured during steady-state submaximal exercise at 50 W (HR50), whereas resting heart rate decreased only by 2.8 bpm.[1] However, the HR50 training response (ΔHR50) was characterized by large interindividual variation: The responses ranged from a decrease of 42 bpm to an increase of 12 bpm. The strongest predictors of ΔHR50 were baseline HR50 and familial aggregation: Baseline HR50 explained about one third of the variance in ΔHR50, whereas maximal heritability estimate of ΔHR50 (adjusted for age, sex, body mass index, and baseline

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HR50) reached 34%.[2] Furthermore, complex segregation analysis supported the hypothesis of a major dominant gene effect on ΔHR50 in the same set of families.[3]

These observations support the hypothesis that genetic factors are involved in ΔHR50 regulation. Subsequently, we performed a genome-wide linkage scan to identify genomic regions that may harbor genes and DNA sequence variants affecting exercise training-induced changes in HR50.[4] The strongest evidence of linkage (logarithm of the odds [LOD] score=2.10) for ΔHR50 was detected on chromosome 2q34 in these HERITAGE families. Herein, we describe fine mapping of the 10 Mb quantitative trait locus (QTL) on 2q34 and provide evidence that functional DNA sequence variant in the cAMP-responsive element-binding protein 1 (*CREB1*) gene locus is strongly associated with ΔHR50 and explains a large proportion of the QTL variance. Moreover, we show that *CREB1*, together with 5 additional loci within the QTL region, fully accounts for the original linkage signal.

Methods

Subjects

The HERITAGE Family Study design, inclusion criteria, and protocol have been previously described.[5] Complete training response data were available for 472 white subjects (229 men and 243 women) from 99 nuclear families. All subjects were healthy and sedentary at baseline. Sedentary was defined as no regular physical activity over the previous 6 months. The study protocol had been approved by the institutional review boards at each of the 5 participating centers of the HERITAGE Family Study consortium. Written informed consent was obtained from each participant.

Exercise Training Program

Subjects completed a 20-week endurance training program (3 days per week for a total of 60 exercise sessions) under supervision using Universal Aerobicycle (Cedar Rapids, Iowa) that was monitored electronically by the Fit Net system to maintain the participants' heart rates at levels associated with fixed percentages of their VO_2. The training program started at the heart rate associated with 55% of VO_2 for 30 minutes per session and gradually increased to 75% for 50 minutes per session during the last 6 weeks of training. All training sessions were supervised on site, and adherence to the protocol was strictly monitored.[6]

Submaximal Exercise Test

Before and after the 20-week training program, each subject completed 2 submaximal exercise tests on separate days. Submaximal exercise tests at 50 W and at 60% of VO_2 were conducted on a cycle ergometer. Subjects exercised 8 to 12 minutes at an absolute work load of 50 W and at a relative power output equivalent to 60% of VO_2, with a 4-minute period of seated rest between the exercise periods. Heart rate was monitored throughout the test with an ECG, and 2 heart rate values were recorded once steady state had been achieved. The heart rate values used in this article represent in each case the mean of 2 submaximal tests at 50 W (HR50), both before and after training. A detailed description of the exercise test methodology has been reported previously.[7] The reproducibility of the submaximal exercise heart rate measurements was very high: Coefficient of variation and intraclass correlation were 4.7% and 0.90, respectively, among the subjects used for the fine-mapping studies.[7]

SNP Selection and Genotyping

Genomic DNA was prepared from immortalized lymphoblastoid cell lines by commercial DNA extraction kit (Gentra Systems, Inc, Minneapolis, Minn). The single-nucleotide polymorphisms (SNPs) were selected from the Caucasian data set of the International HapMap consortium (data release 21a, January 2007) using the pairwise algorithm of the Tagger program.[8] The entire target region was screened for linkage disequilibrium (LD) clusters using a pairwise LD threshold of $r^2 \geq 0.80$ and minimum minor allele frequency of 10%. In addition, each gene (defined as exons, introns, and 20 kb of 5′ and 3′ untranslated regions) annotated in the NCBI Build 36.3 database on the region was screened using $r^2 \geq 0.90$ and minor allele frequency >5%. The HapMap data set contained 8812 eligible SNPs within the target region and Tagger identified 1556 tag SNPs. The Illumina SNP assay scoring algorithm identified 20 SNPs that were predicted not to be genotyped successfully. Thus, the final number of SNPs selected for genotyping was 1536.

Genotyping of the SNPs was done using the Illumina (San Diego, Calif) GoldenGate chemistry and Sentrix Array Matrix (1536-plex array) technology on the BeadStation 500GX. Genotype calling was done with the Illumina BeadStudio software, and each call was confirmed manually. Of the 1536 SNPs, 1450 (94.4%) were genotyped successfully. For quality control purposes, 5 CEPH control DNA samples (NA10851, NA10854, NA10857, NA10860, and NA10861; all samples included in the HapMap Caucasian panel) were genotyped in duplicate. Concordance between the replicates and the genotypes from the HapMap database was 100%. No mendelian errors were detected among the HERITAGE families. Finally, 2 gender-specific control markers included in each Illumina GoldenGate assay agreed 100% with the gender of the subjects.

Functional Studies With SNP rs2253206

Functional testing of the *CREB1* rs2253206 was performed by generating two 150-bp constructs, one for each rs2253206 allele. The constructs were generated by polymerase chain reaction using DNA from a heterozygous subject. Amplicons were cloned directionally into the pGL3-basic luciferase expression vector at the *Sac I* (AGC ACG CTA GCC CTT ACC TGC ACA AT) and *Xho I* (GTC TGC TCG AGG CTC TCA CTT CAG GG) restriction recognition sites. The mouse skeletal muscle C2C12 cell line was used to represent the muscle-specific expression for *CREB1*. Cell culture was performed as previously described.[9] Cells were transfected by electroporation (Lonza, Amaxa Nucleofector, Walkersville, Md). Cells were cotransfected with the construct and renilla. Luciferase was measured on a Berthold LB 9507 luminometer as previously described.[10] The data shown represent 5 replicates per experiment from 3 independent experiments.

Statistical Analyses

HR50 training response phenotype was adjusted for the effects of sex, age, body mass index, and baseline HR50 using stepwise multiple regressions, retaining only the terms significant at the 5% level.[11] The residuals from this regression were then standardized to 0 mean and unit variance, which constituted the analysis variables.

Single-SNP associations with ΔHR50 were analyzed using a variance component and likelihood ratio test–based procedure in the QTDT software package.[12] The total association model of the QTDT software utilizes a variance-components framework to combine phenotypic means model and the estimates of additive genetic, residual genetic, and residual environmental variances from a variance-covariance matrix into a single likelihood model.[12] The evidence of association is evaluated by maximizing the likelihoods under 2 conditions: The null hypothesis (L0) restricts the additive genetic effect of the marker locus to zero ($\beta a=0$), whereas the alternative hypothesis does not impose any restrictions on βa. Twice the difference of the log likelihoods between the alternative and the null hypotheses {2[ln (L1)−ln (L0)]} is distributed as χ^2 with 1 *df* (difference in number of parameters estimated). Multiple testing adjustments of the single-SNP association *P* values were done using the p_ACT program.[13] This method takes into account the nonindependence of the tests because of LD between the SNPs and correlations between tested traits. It has accuracy comparable to computationally more intensive permutation or simulation-based tests.[13]

The potential contribution of multiple SNPs on ΔHR50 was tested using standard regression models. All SNPs that showed nominal *P* values <0.02 in the single-SNP analyses were first tested using the

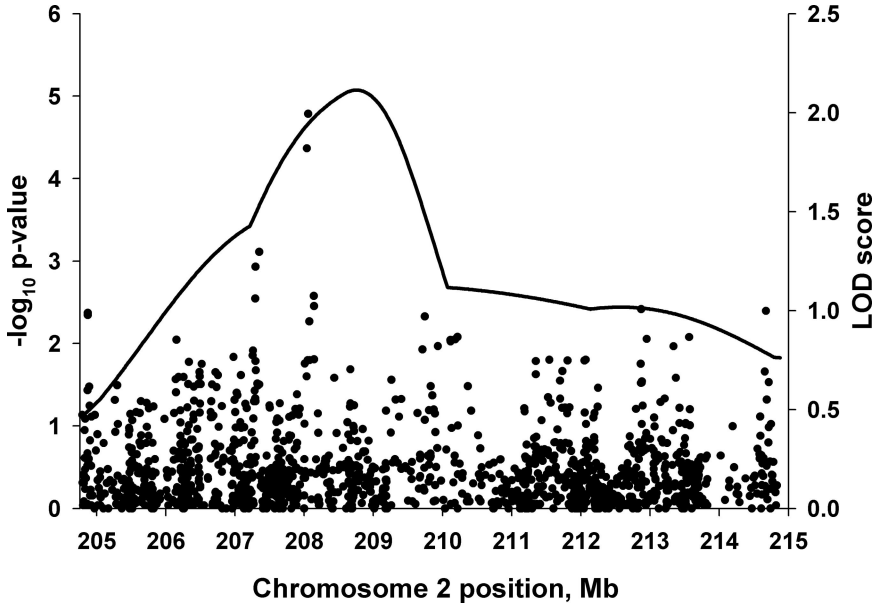

Figure 1. Summary of the linkage and association results. *P* values (presented as −log10) from the single-SNP association analyses for HR50 training response are presented as black dots; the black line shows linkage signal from the original multipoint linkage scan. *x*-axis shows physical map location on chromosome 2, left *y*-axis *P* values for the association tests, and right *y*-axis LOD scores for the linkage analyses.

backward selection method to filter out redundant SNPs. All SNPs that remained in the backward model (at $P<0.1$) were then analyzed using a regression model with a forward selection method.

Linkage analyses were performed using a multipoint regression–based model as implemented in MERLIN.[14,15] In conditional linkage analyses, the SNPs derived from the association analyses were used as covariates. If an SNP contributes to the QTL-specific genetic variance, the evidence of linkage should weaken when the effect of the SNP is accounted for. First, all 9 SNPs (derived from the multivariate regression model) were tested individually, and the marker with the strongest effect on the LOD score was retained in the model. Next, the remaining 10 SNPs were tested individually, and the marker that induced the greatest reduction in the LOD score was retained. The same process was repeated with the remaining SNPs as long as the LOD score reached the nadir.

Results

The maximum LOD score of 2.10 on chromosome 2q34 was detected with marker D2S154 in the original genome-wide linkage scan.[4] The 1−LOD target region covered 10 Mb between 205 and 215 Mb and was fine-mapped by genotyping 1450 tag SNPs. The total association model detected the strongest associations with SNPs rs2253206 ($P=1.6\times10^{-5}$) and rs2360969 ($P=4.3\times10^{-5}$) located 2.6 and 22.6 kb upstream of the *CREB1* gene (pairwise LD between the SNPs $r^2=0.83$; Figure 1 and supplemental Table I) and about 400 kb from the linkage peak with marker D2S154 (Figure 1). Both markers remained significant after controlling for multiple testing (rs2253206: $P_{ACT}=0.01$; rs2360969: $P_{ACT}=0.028$). The

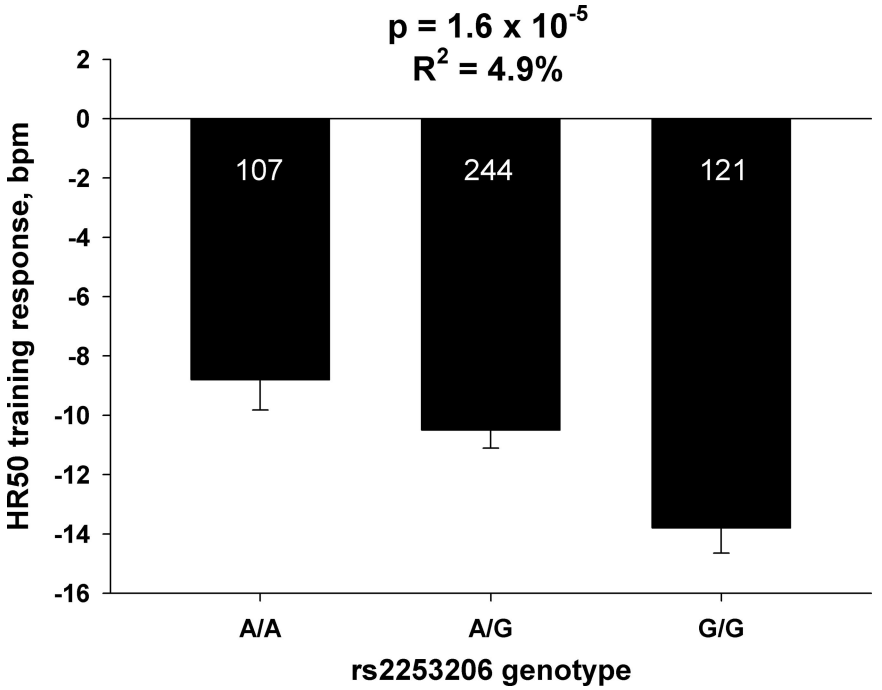

Figure 2. Association between the *CREB1* SNP rs2253206 and HR50 training response in whites of the HERITAGE Family Study. Number of subjects for each genotype is shown within the bars.

Table. Results of the Multivariate Regression Model With Forward Selection

Step	SNP	Partial R^2	Model R^2	P	Map	Gene
1	rs2253206*	0.0545	0.0545	<0.0001	208, 100, 223	*CREB1*
2	rs4675639*	0.0307	0.0852	<0.0001	207, 391, 182	*FASTKD2*
3	rs3768816*	0.0258	0.111	0.0003	210, 257, 423	*MAP2*
4	rs7597126	0.0208	0.1318	0.0009	214, 717, 603	*SPAG16*
5	rs13387495	0.0166	0.1485	0.0028	212, 993, 302	*ERBB4*
6	rs6435639	0.0142	0.1626	0.0054	212, 111, 568	*ERBB4*
7	rs10932460*	0.0147	0.1773	0.0042	213, 608, 717	*IKZF2*
8	rs1876048*	0.0137	0.191	0.0055	212, 914, 094	*ERBB4*
9	rs11681709*	0.0099	0.2009	0.0169	206, 197, 328	*PARD3B*

*SNP was also retained in the final model of the conditional linkage analysis.

rs2253206 common allele homozygotes (G/G) and heterozygotes had ≈57% and 20%, respectively, better ΔHR50 than the minor allele homozygotes (Figure 2). In single-SNP analyses, rs2253206 explained 4.9% of the variance in HR50 training response. The frequency of the rs2253206 minor allele was 47.8% among all HERITAGE subjects, whereas the frequencies were 41.0% and 58.4% among the HR50 best responders (bottom quartile of the HR50 response distribution) and worst responders (top quartile; see supplement Table I), respectively.

Although SNP rs2253206 was strongly associated with ΔHR50, a portion of the QTL-specific variance remained unaccounted for. To explore the potential contribution of additional markers, all SNPs that showed nominal P values <0.02 in the single-SNP analyses (39 SNPs total) were selected for multivariate regression analyses. The SNPs were first analyzed using a backward selection method to filter out redundant SNPs (because of strong pairwise LD among the SNPs). The backward selection model retained 13 SNPs with P values <0.1, and these markers were then analyzed using a regression model with forward selection. Results of the final regression model are summarized in the Table. The most significant marker was rs2253206, explaining 5.45% of the ΔHR50 variance. Eight other SNPs each contributed at least 1% of the variance, and, collectively, the 9 SNPs explained 20% of the ΔHR50 variance. This contrasts well with the overall genetic heritability of the phenotype (h^2=34%).

Finally, contribution of the 9 SNPs from the regression model to the original linkage signal was tested using conditional linkage analysis. Individually, the SNPs weakened the linkage signal by 0 to 0.45 LOD score units, but none of them by themselves was able to eliminate the original linkage. The nadir of the LOD score was reached with a combination of 6 SNPs [rs2253206 (*CREB1*), rs4675639 (*FASTKD2*), rs3768816 (*MAP2*), rs1876048 (*ERBB4*), rs11681709 (*PARD3B*), and 10932460 (*IKZF2*)]: The LOD score was reduced from 2.10 to 0.41 (supplemental Figure I). Addition of the remaining 5 SNPs (either one at a time or all simultaneously) did not affect the LOD score.

SNP rs2253206 is located about 2.6 kb upstream of the first exon of *CREB1*. We tested the effect of rs2253206 on promoter activity by expressing the genotype-specific constructs in C2C12 cell line. As shown in Figure 3, the A-allele rs2253206 was associated with greater promoter activity than the common allele (G).

Discussion

The main finding of our study is that DNA sequence variation in the *CREB1* gene locus is strongly associated with submaximal exercise heart rate training response and explains a large portion of the genetic variation associated with the QTL on chromosome 2q34. However, our results also suggest that *CREB1* is not the only locus contributing to the QTL variance: At least 5 other loci were needed to account fully for the original linkage signal. The strongest evidence of association with HR50 training response was observed with 2 SNPs located in the 5′ region of the *CREB1* gene: These associations remained statistically significant after controlling for multiple testing. The minor allele homozygotes of SNP rs2253206 had on average 1.7 and 5.0 bpm smaller improvements in HR50 than the heterozygotes and major allele homozygotes, respectively, and the frequency of the minor allele was considerably higher in the HR50 worst responders (58.4%) than in the best responders (41.0%).

CREB1 is an abundantly expressed regulator of gene expression that has been shown to be involved in the regulation of several physiological functions. *CREB1* affects target genes by binding to a specific cAMP response element on the promoter region of target genes, thereby activating gene transcription. The *CREB1* protein may also exert its

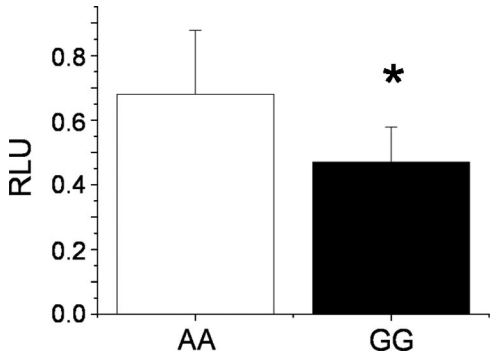

Figure 3. Functional analyses with *CREB1* variant rs2253206. Transient transfection data of rs2253206 promoter reporter constructs in C2C12. Each bar represents mean±SD of 5 replicates for the corresponding genotype (*P<0.05). RLU indicates relative luciferase activity of light units adjusted by renilla.

action by interacting directly with target proteins. *CREB1* has been shown to be a key mediator of contraction-transcription coupling in excitable cells.[16] This process plays an important role in the maintenance of late-phase long-term synaptic potentiation, a cellular model for long-lasting memory formation in neurons.[17] A similar *CREB1*-dependent mechanism is also involved in the generation of long-term cardiac memory, a process leading to adaptation of ventricular repolarization (indexed by electrocardiographic T wave) to ventricular pacing. Long-term pacing downregulates nuclear *CREB1*, which leads to reduced expression of *KCND3* and *KCNIP2*, the main components of potassium channel contribution to transient outward potassium current in ventricular cardiomyocytes.[18,19] Given that exercise training represents "physiological" cardiac pacing, a cardiomyocyte-specific mechanism such as cardiac memory is an appealing hypothesis to explain our findings on *CREB*1 and submaximal exercise heart rate training response. However, given that training-induced changes in neuronal plasticity seem to contribute to cardiovascular adaptation to regular physical activity,[20] we cannot rule out the central nervous system as a site of *CREB1* action in heart rate regulation.

Our functional studies revealed that the rs2253206 common "G" allele is associated with significantly lower promoter activity than the minor "A" allele. Algorithmic analysis (Alibaba 2.1) of the region encompassing SNP rs2253206 identified a predicted binding site for the CCAAT enhancer-binding protein-alpha (C/EBPα) transcription factor. Substitution of the "G" with the minor "A" allele resulted in loss of the predicted binding site for C/EBPα. C/EBPα can lead to suppression of stem cell proliferation[21] and inhibition of cell growth.[22] The increase of promoter activity associated with the "A" allele is therefore consistent with the predicted loss of the binding site for C/EBPα. We did not have access to plasma or ideally cardiac tissue preparations to assess the functional impact of the "A" allele on the expression levels of *CREB1*, but our promoter analysis data predict an elevation of *CREB1* for the "AA" homozygotes (potentially due to loss of the C/EBPα motif).

The main reason cited in the literature for the less than optimal success in fine mapping of complex trait linkage QTLs is the poor resolution of linkage analysis to detect polygenic and even oligogenic effects. Our findings tend to agree with this explanation. The original LOD score (2.10) on chromosome 2q34 was less than the traditional threshold for genome-wide significance (LOD=3.0), and our conditional linkage analysis results support the hypothesis that multiple loci within the QTL region contribute to the linkage signal. Although *CREB1* SNPs showed clearly the strongest associations with ΔHR50 and were the only SNPs that remained significant after multiple testing correction, these SNPs together with 5 additional SNPs explained nearly all the linkage evidence (LOD score of 2.10 went down to 0.41). However, the genes tagged by the additional 5 SNPs are not only positional candidates, but some of them also have potential functional relevance to ΔHR50. For example, *ERBB4* has been shown to be involved in neuregulin-1–induced formation of the cardiac conduction system as well as in cardiomyocyte proliferation and repair mechanisms after myocardial injury.[23,24]

The strengths of our study include highly standardized submaximal exercise heart rate phenotype, fully controlled exercise training program with excellent compliance, and systematic screening of the entire QTL region with tag SNPs. Both before and after the training program, submaximal exercise tests at 50 W were performed twice on separate days, and heart rate was recorded during the tests after steady state was reached. This allowed us to decrease random phenotypic variation and, consequently, to improve our chances of detecting genetic variation more precisely. The standardized exercise intervention gave an opportunity to investigate long-term heart rate adaptation to regular physical activity. This has both physiological and public health relevance, because regular physical activity, as implemented in the HERITAGE intervention, is a central part of the current national and international guidelines for a heart-healthy lifestyle. However, to utilize physical activity more effectively in promotion of heart health, we must understand the factors that contribute to the interindividual differences in responsiveness to regular physical activity.

It should be noted that our findings are specific for submaximal exercise heart rate adaptation to regular exercise. Both linkage and association signals were detected with ΔHR50 but not with heart rate response to acute exercise (HR50 at baseline) or with resting heart rate phenotypes (baseline or response to training; data not shown). This clearly indicates that the genetic component related to chromosome 2q34 QTL is specific for long-term adaptation rather than acute responsiveness. The fact that the signal was detected with submaximal exercise rather than resting heart rate adaptation may reflect more stringent regulation of resting heart rate than exercise heart rate in sedentary individuals. It is also possible that in steady state, low-intensity exercise is a more efficient way than resting to standardize heart rate measurement, as suggested by better reproducibility of the submaximal exercise measurements [coefficient of variation: 4.7% (HR50) versus 7.3% (HRrest); intraclass correlation: 0.90 (HR50) versus 0.74 (HRrest)].

The weakness of our study is the lack of replication studies. Recent successful genome-wide association studies have shown the importance of validation of initial genetic associations in other studies with comparable design, subject characteristics, and phenotype measurements. Although replication is a fairly straightforward procedure in observational, cross-sectional studies, it is a major challenge for intervention studies such as ours. Especially, study design and intervention-related details make it particularly difficult to find suitable replication cohorts. For example, the HERITAGE Family Study is the largest and most carefully standardized exercise training study ever done; other studies with sufficiently large sample sizes, exercise training program, subject compliance, and phenotype measurements do not exist, making replication studies a real challenge at the moment. However, with an increased interest in gene by physical activity interactions on various health outcomes, it is likely that bigger and better exercise intervention studies will be undertaken in the future, given that appropriately controlled and standardized intervention study is the most powerful approach to test such interactions.

In summary, our data indicate that DNA sequence variation in the *CREB1* gene locus is strongly associated with submaximal exercise heart rate response to exercise training and that SNP rs2253206 located in the 5′ region of *CREB1* modifies promoter activity. Although *CREB1* explains a large proportion of the QTL-specific variance, additional loci on chromosome 2q34 are needed to fully account for the original linkage signal, an observation that is well in line with the polygenic nature of exercise heart rate regulation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Regular physical activity is a cornerstone of a heart-healthy lifestyle. Exercise training improves cardiac function and several cardiovascular disease risk factors, including ability to perform physical tasks at a given work load with a lower heart rate. However, the cardiovascular benefits of regular physical activity are not equally distributed among individuals, because some exhibit marked improvements whereas others may show little or no changes. Our previous work has shown that interindividual variation in responsiveness to training aggregates in families. Herein, we show that DNA sequence variation in the cAMP-responsive element-binding protein 1 gene locus is a strong genetic predictor of variation in exercise training–induced changes in submaximal exercise heart rate, explaining about 5% of the total variance. Better understanding of the predictors of high and low responsiveness to regular physical activity has physiological, clinical, and public health relevance. Such information would help to identify those individuals who would derive the greatest health benefits from exercise training as well as patients who would need other therapeutic options (diet and medication) to support a physically active lifestyle.