cAMP Responsive Element Binding Protein 1
A Missing Link for Heart Rate Regulation?

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Life scientists, especially those of us from a previous generation (or two), were trained to focus our efforts on generating large mean differences between groups or large changes with interventions while minimizing variability. The goal was to maximize effect size, thereby optimizing the chance of generating a statistically significant difference or change that, in turn, increased the odds that the data would be publishable. And, yes, even “way” back then, publications were still the “coin of the realm.”

However, investigators from more recent generations, and even some from previous generations, have finally begun to realize that the variability among individuals or their responses to interventions are also important. This realization was quite pointedly brought to my attention in an initial discussion with a geneticist about a possible collaboration. He asked, “How does blood pressure change with exercise training?” I responded, “Our previous reviews indicate that the average change in systolic and diastolic blood pressure with exercise training is …” at which point he stopped me and asked, “No, what was the variability in the responses?” Not surprisingly, given my training in the previous generations as a life scientist, I did not have an answer. Thus began my path to recognizing the importance of the interindividual variability in responses to exercise training. This variability took on even more importance at that time in light of the relatively recently initiated Human Genome Project and its potential to produce a new era of personalized medicine.

That thought-provoking question spurred me to revisit some of my previous data but now with a focus on the interindividual variability for the exercise training-induced responses of the cardiovascular (CV) disease risk factors that I studied throughout my career. Sure enough, interindividual variability in these responses is substantial! Most of us missed this potentially critical point because of our tunnel-vision focus on mean values.

By far, the best study to address the interindividual variation in response to exercise training is the HERITAGE Family Study1 from which the data for the present study were generated. HERITAGE recruited 2-generation black and white families and measured a number of CV and CV disease risk factor phenotypes before and after 20 weeks of highly standardized endurance exercise training. HERITAGE remains the only study with the necessary family structure and sample size to generate heritability estimates for training-induced response phenotypes, to perform linkage analyses, and to identify novel chromosomal loci related to training-induced responses.

Probably the most frequently and best characterized effect of endurance exercise training is an increased maximal aerobic capacity (VO2max). However, even with this classical training response, there is substantial interindividual variation. HERITAGE reported a mean VO2max increase of 384 mL/min with training in 720 individuals.2 However, the SD around this mean was 202 mL/min; thus, it would be expected that ≈115 of the 720 individuals would have increased their VO2max training by <180 mL/min, whereas another ≈115 would have increased VO2max by >585 mL/min. Clearly, not everyone exhibits the same VO2max response to exercise training.

Another generally consistent finding, at least with fairly prolonged training programs, is increased plasma high-density lipoprotein cholesterol (HDL-C) levels. But here the variation is even more dramatic. Previously from HERITAGE, Leon and coworkers3 reported a significant overall ≈4% increase in HDL-C with training. However, the lowest quartile of respondents actually had an ≈9% average decrease in HDL-C levels with training, whereas the highest responding quartile experienced an 18% average increase. In our laboratory, ≈33% of middle- to older-aged men and women actually decreased or did not change HDL-C levels, whereas another ≈33% each increased HDL-C levels by >7 mg/dL with a highly standardized 26-week exercise training program and a low-fat isocaloric diet.4 The challenge for personalized medicine is to identify these optimal versus suboptimal responders a priori so that the benefits of that intervention can be targeted directly to those who will benefit the most in terms of exercise outcome.

Genomics, which is proposed as the backbone of personalized medicine, can potentially help in this regard because of the sequencing of the human genome and the cataloging of single-nucleotide polymorphisms (SNPs), haplotypes, insertions and deletions, and copy number variations across the human genome. Clearly, some of these variations are of direct Mendelian and pathological significance, such as in cystic fibrosis. However, what about the other millions of genetic variations that do not result in a direct Mendelian pathological condition? Might they contribute to other less-obvious phenotypic differences between individuals? Might they de

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termine how an individual responds to an environmental stressor, such as heat, or a dietary alteration, such as a switch from a high- to a low-fat diet? Or could some of these other genetic variations affect how individuals respond to increased levels of physical activity?

The present ground-breaking work by Rankinen, Bouchard, and HERITAGE addresses another classical and highly clinically relevant CV response to exercise training: a reduction in heart rate (HR) at a given submaximal work rate after versus before training. This work is clinically relevant because virtually all rehabilitation programs for various CV and metabolic diseases base their exercise prescriptions on HR responses to exercise. Perhaps even more importantly, this adaptation generally is one of the first that patients experience when starting an exercise program. After a few weeks of exercise, walking at 3.2 mph on a level treadmill now elicits an HR of 110 bpm, whereas the patient’s HR was 116 bpm only a few weeks previous. Such a response is also clinically significant because the lower HR reduces the work of the heart and, hence, improves the balance between oxygen supply and demand.

Thus, quantifying the change in HR at a given work rate in response to exercise training is important on a number of levels. In the present study, Rankinen and Bouchard report that the 20-week HERITAGE training program on average reduced HR by a fairly substantial 11.3 bpm at a 50-W work rate. However, that variability issue once again raised its head with one individual reducing HR by 42 bpm while another actually increased HR at this work rate by 12 bpm with training. In fact, the SD of this response was 10 bpm, indicating that ~75 of the study’s ~470 individuals decreased exercise HR by <~1 bpm (with a fair number of them actually increasing their HR with training), whereas a similar number each decreased HR by >21 bpm with training. Previous studies from HERITAGE indicated that the heritability of this response to training was 0.34 and that this was due to a major dominant gene effect.

Subsequently, HERITAGE assessed genome-wide linkage of these responses and found the strongest linkage on chromosome 2q34 (logarithm of odds score, 2.10). The present study then typed 1450 tagSNPs distributed over 10 Mb across 2q34 to identify loci underlying these differential HR responses to exercise training and succeeded—perhaps beyond their wildest dreams!

In their total SNP association model, two SNPs slightly upstream of the cAMP responsive element binding protein 1 gene showed the strongest association with HR response to training. Importantly, the minor allele frequency for the SNP with the strongest association (rs2253206) was 48%; thus, the variant is common and, therefore, could affect a population’s overall response to exercise training. Furthermore, its effect was sizable, with G homozygotes and heterozygotes at this locus having ~60% and ~20% greater HR reductions, respectively, with training than A homozygotes. This variant accounted for a rather astounding ~5% of the total interindividual variance in this response to exercise training. Additionally, consistent with its in vivo effects, promoter activity varied among C2C12 cell lines transfected with the three different genotypes at this locus. Finally, although the rs2253206 variant had a substantial effect, 8 other SNPs each accounted for >1% of the interindividual variation in this response. After adding these SNPs to the regression model, the genetic component accounted for, again, a rather astounding 20% of the total interindividual variance.

This study joins two others as the most important and influential publications from the already-classic HERITAGE Family Study. These previous studies used the same approach as the present study: They first found significant heritability for the phenotype of interest, identified novel loci potentially underlying this phenotype using genome-wide linkage analyses, fine mapped the chromosomal locus with the highest linkage, performed numerous SNP statistical association analyses, and performed cell culture studies to assess the molecular effects of their novel SNPs. In both previous studies, the phenotype of interest was the training-induced change in submaximal exercise stroke volume, and the novel genes that they identified were titin and kinesin-1 heavy chain. Neither of these 2 genes would have been considered candidate chromosomal loci to underlie this phenotype. Similarly, cAMP responsive element binding protein 1, found to play such an important role in the present study, would not have been on any list as a potential candidate gene affecting the training-induced change in submaximal exercise HR. On a much larger scale, the overall principle of identifying novel mechanisms involved in the regulation of heritable exercise-training response phenotypes clearly has been validated by these three sets of findings.

In the initial genomic studies, the overarching hope was that a small number of susceptibility genes would each have a substantial impact on a person’s risk of developing such generally non-Mendelian pathologies as type 2 diabetes, hypertension, and obesity. This hope extended to virtually all genomic studies, and initial attempts were focused on finding the few genes that had a substantial impact on a given phenotype, perhaps, as in this study, the response of an important and clinically relevant phenotype to exercise training. Although the “few genes-large effects” genetic paradigm has proven not to be the case for most susceptibility genes related to pathologies and physiology, the present study has identified a single gene with a substantial impact on the training-induced change in submaximal exercise HR response. As such, these findings provide a strong initial step toward the application of personalized medicine to the optimal prescription of exercise training that might well enhance a person’s adherence and responses to an exercise-training intervention.


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