Does your (genetic) alphabet soup spell “runner”?

Marcas M. Bamman
Departments of Physiology and Biophysics, Medicine, and Nutrition Sciences, University of Alabama at Birmingham, Birmingham, Alabama

LOW AEROBIC CAPACITY [i.e., low maximum oxygen consumption ($\dot{V}O_2_{max}$)] has been recognized as a significant predictor of disease (e.g., cardiovascular disease) risk, as well as mortality, for more than two decades (3). This is one of the important relationships supporting the impetus for exercise training as medicine, a prominent healthcare initiative co-sponsored by the American College of Sports Medicine and the American Medical Association (1). Furthermore, the associations between aerobic capacity and disease risk have led to the development of valuable animal models to study disease risk mechanisms in detail (5, 7, 8, 10). Endurance exercise training of sufficient volume, duration, frequency, and intensity is the most effective means of improving $\dot{V}O_2_{max}$ and is widely considered an integral component of any prescription for exercise as preventative medicine. Unfortunately, however, not all individuals adapt optimally to such training; i.e., they fail to realize the magnitudes of improvement in $\dot{V}O_2_{max}$ that may mitigate the morbidity and mortality risk associated with low aerobic capacity (4). Underlying causes of this wide range of interindividual variability are poorly understood. In their novel and impactful new work, Timmons et al. (9) may have identified key genetic links to such variation. The authors present a stepwise and fairly comprehensive approach to defining a 29-gene expression signature in untrained skeletal muscle that remarkably explained >50% of the variance in exercise-induced $\dot{V}O_2_{max}$ gains ($r^2 = 0.58$) and led to the targeted identification of 11 single-nucleotide polymorphisms (SNPs) that also account for a meaningful proportion of this between-subjects variation in aerobic capacity “trainability.”

In a unique design, Timmons et al. (9) studied muscle biopsy specimens from two independent endurance-training studies. First, they revealed the 29-gene molecular “predictor” signature in a group of 24 sedentary young men who completed 6 wk of a typical endurance cycling program (4 days/wk, 45 min/day, at 70% of pretraining $\dot{V}O_2_{max}$). They then validated the signature in a group of young active subjects who performed combined interval and continuous endurance training for 12 wk. Finally, the authors took advantage of blood samples from a large cohort ($n = 473$, the HERITAGE Family Study) who exercise trained 3 days/wk for 20 wk (intensity = 55–75% of maximal heart rate) to identify genes within the 29-gene signature and from a panel of 10 candidate genes that had been evidenced previously in the HERITAGE Family Study through genome-wide scans and fine mapping studies that displayed genetic variants (SNPs) that relate to the interindividual variability in $\dot{V}O_2_{max}$ gain. A key finding in the first two studies was that levels of expression for most all mRNAs in the signature were not altered by exercise training, indicating a truly predictor signature based on preestablished variation in gene expression. The predictor genes fit nicely into a network related to developmental processes. Analysis of polymorphic variants using the HERITAGE cohort revealed six genes from the predictor signature plus five from the previously identified candidate genes that displayed SNPs associated with gains in $\dot{V}O_2_{max}$. These 11 SNPs accounted for 23% of the variance in $\dot{V}O_2_{max}$ gain.

The findings of Timmons et al. (9) are remarkable: they reveal, for the first time, an underlying genetic link to individual adaptability for a complex and multifactorial physiological trait (aerobic capacity). Even more remarkable is the finding that nearly one-fourth of an individual’s adaptability is driven by genotypic variation within a relatively small cluster of genes. The authors are to be commended for the stepwise and novel approach by which genotyping was directed to those genes that were first identified as members of the RNA-based molecular signature with the power to predict gains in $\dot{V}O_2_{max}$. The implications of this work are far-reaching. The strategy itself may prove promising for identifying molecular mechanisms that underlie between-subjects heterogeneity of responsiveness or adaptability to a wide array of stimuli, including exercise training. Clearly, such heterogeneity is not limited to endurance exercise adaptation, as we recently reported highly variable responsiveness to resistance training as well (2, 6).

In efforts to identify molecular regulators of adaptation during exercise training, we and several others have focused attention on mRNAs and/or proteins that were responsive to exercise with altered levels. In fact, differences in the magnitude or direction of such molecular changes have been hypothesized to play a role in differential adaptations between groups on the basis of independent variables such as age or sex. While such findings should not be discounted, it is certainly noteworthy that Timmons et al. (9) reported training-induced changes in the levels of expression (>1.5-fold) for ~800 genes (the “training-responsive transcriptome”), with many of the differentially expressed genes behaving similarly in high and low responders. On the other hand, expression levels of the 29 predictor genes were relatively stable before and after training, and it was individual variability in the pretraining levels, combined with 11 genetic variants, that proved to be valuable predictors of adaptability.

An important outcome of this work not to be overlooked is that the predictor signature “held up” when applied to a more physically active cohort (group 2) that was treated with a substantially different and more intensive training stimulus (vs. group 1), i.e., one that incorporated high-intensity interval training. Validation of the predictor model in group 2 thus minimizes the possibility that low responders in group 1 might have better responded to an alternative training stimulus. Unfortunately for the low responders in these studies, the predetermined (genetic) alphabet soup just may not spell “runner.”

Overall, this work may present a paradigm shift in how investigators approach studies of adaptability involving com-
plex phenotypic traits. As a result of this article, greater attention may be focused on the concept of a baseline or pretraining predictor profile combining mRNA expression profiling with genetic polymorphism. The approach may also prove useful in the expanding arena of personalized medicine. This work is truly an outstanding contribution that will likely inform and inspire future directions.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

REFERENCES